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UNOFFICIAL TRANSCRIPT*
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING
February 15, 2006
Marriott Hotel Seatac
9:00am – 4:00pm

Committee Attendance:
Angelo Ballasiotes, Pharm D
Robert Bray, M.D.
Alvin Goo, Pharm D
Jason Iltz, Pharm D
Janet Kelly, Pharm D
Daniel Lessler, M.D.
T. Vyn Reese, M.D.
Patti Varley, ARNP
Kenneth Wiscomb, PA-C

9:00 a.m. - Committee came to order.

WELCOME & INTRODUCTIONS

Jeff Graham, MD: Susan, can you hear us? Susan, can you hear us?

Susan Carson, MPH: They can hear me, but I can't hear them. See you later.

Woman: Can you hear me?

Susan Carson, MPH: I can hear you now.

Woman: Susan?

Susan Carson, MPH: Yeah.

Woman: Hang on just a second.

Susan Carson, MPH: Okay.

Woman: I'm going to ask you to…see if you can hear the speakers in the room. I'm on a telephone. So I'm going to ask them to speak to you on the speakers. Hang on a second okay?

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* For copies of the official audio taped record of this meeting, please contact Regina Chacon at (206)521-2027 pdp@hca.wa.gov.

Susan Carson, MPH: Okay.

Jeff Graham, MD: Susan, this is Jeff Graham. Can you hear me now?

Susan Carson, MPH: Not really, no.

Jeff Graham, MD: Actually, we could go ahead and start with your presentation…

Susan Carson, MPH: Yeah, it sounds very garbled.

Jeff Graham, MD: So that we're ready when we want questions. So why don't we do that.

Woman: We're going to go ahead, Susan, and ask you to start your presentation and we'll continue to work on the technological end here. But just go ahead. Okay?

Susan Carson, MPH: Okay. Great. So you have my slides?

Woman: Yes, we do.

Susan Carson, MPH: Okay. So starting with the first slide I'm presenting the drug class review on new sedative hypnotics. Can you still hear me?

Jeff Graham, MD: Yes.

Susan Carson, MPH: It sounds like I got cut off. I'm going to hang up and call back.

Woman: Is Susan on? Jeff, speak into the microphone and let me see if I can hear you. Okay?

Jeff Graham, MD: Can you hear me?

Susan Carson, MPH: Hi, I'm back.

Woman: Hi, Susan. We still have the same difficulty, but go ahead and start your presentation.

Susan Carson, MPH: Okay. I heard a beep and then nobody answered me so I thought I got cut off.

Woman: Right. That was me cutting off my phone. That was a mistake. Go ahead.

Susan Carson, MPH: All right. Great. So we'll move onto slide number two, please. It shows our searches. We conducted searches through April or May 2005 and these electronic searches were supplemented by hand searches, of reference lists, of relevant articles. We also received dossiers from two companies—the makers of Zolpidem and Eszopiclone. And also FDA reviews that were available on the FDA web site provided information to supplement published reports of head-to-head trials.

Next slide. Data collection and analysis we found usual DERP methods assessed studies for inclusion and rated their quality using pre-defined criteria. When sufficient information was available we calculated the weighted mean difference between treatments or between treatment and placebo and we conducted meta analyses when

study populations and interventions were similar and when there was not significant statistical heterogeneity among trials.

Next slide shows the included drugs. We included four newer sedative hypnotics—Zaleplon, Zolpidem, Zopiclone and Eszopiclone. One of these drugs, Zopiclone is available in Canada, but not the U.S. and we included it in our report because one of our participating organizations is the Canadian coordinating office for health technology assessment. So I have information about Zopiclone in my presentation, but I will just quickly go over it because I assume you're not interested in that.

Also shown on the slide is the fact that there are some differences among the drugs in their pharmacokinetics. For example, the half-life of the drugs buried from one hour to six and theoretically this could be expected to effect different aspects of insomnia. For example, a drug with a shorter half-life might be effective for sleep latency, but less effective for sleep duration. Also, the recommended starting dose in the elderly is half the adult dose for all of the drugs because of the theoretical risk of increased adverse effects based on increased bioavailability in the elderly.

The next slide shows results of our…an overview of the results of our literature search. We included seven head-to-head trials. One of these has not been fully published, but we supplemented information…sorry, I'm getting feedback. We supplemented information provided in a poster presentation with information from the FDA review and also information submitted by the funder of the study. And to supplement direct evidence from head-to-head trials we also included 31 placebo-controlled trials and 44 active controlled trials of newer sedative hypnotics versus Benzodiazepine or versus Trazodone. These studies were used to make indirect comparisons of the newer sedative hypnotics but comparing Benzodiazepine and Trazodone to the newer drugs was not the focus of our review.

Woman: I'm going to interrupt. Can you hear me?

Susan Carson, MPH: Next slide. It summarizes…this slide summarizes the breakdown of the seven head-to-head trials. There was only one head-to-head study of Eszopiclone versus another newer sedative hypnotic, Zolpidem.

Next slide, which is titled key questions one and two, comparative benefits in [inaudible]. First, the comparison of Zolpidem versus Zaleplon. There are four head-to-head trials in this comparison, two four-week trials that's Eile (1999) and FRY(2000)were conducted in adults younger than age 65 and they had identical designs where they compared three doses of Zaleplon to ten milligrams of Zolpidem.

And then another, a third study, Ancoli-Israel (1999)[inaudible] 1999 was conducted in patients over age 65. In all three of this efficacy trials there was a placebo arm and the reports were then compared to the placebo rather than head-to-head. So the head-to-head comparisons we were able to make were limited because of the limited information provided in the reports.

The fourth head-to-head trial of this comparison Allain 2003(?) was a single dose study and the primary outcome was patient preference for a drug.

So moving on to slide eight, which shows the primary outcome of sleep latency in studies of Zolpidem versus Zaleplon and this outcome was measured at week one, two, three and four. The report results for each of those time periods. In one trial in adults at weeks one through four there was no difference between Zaleplon 5 or 10 mg and Zolpidem 10 mg on the [inaudible] number of minutes to sleep onset. There was a shorter sleep latency with a higher dose of Zaleplon, that's 20 mg, but in the study we had no comparison of Zolpidem. There was no Zolpidem 20 mg so we couldn't compare those two doses.

In the second trial, ILY, the results were mixed depending on the dose and the time period and we were able to look at the comparison to placebo only in this study. So the results were mixed. For example, Zaleplon at all three doses was better than placebo except 5 mg at week four. And for Zolpidem 10 mg weeks two and three were better than placebo, but not week four.

And the third study with sleep latency as the primary outcome with the study in elderly patients and results were similar for the results in the adult studies. There was no difference in sleep latency for Zaleplon 5 mg versus Zolpidem 5 mg, but the higher dose of Zaleplon was better than the 5 mg dose of Zolpidem.

Next slide. Again, Zolpidem versus Zaleplon other sleep outcomes. For sleep durations Zolpidem was better than placebo at all doses and time points up to four weeks. The increases range from 21 to 42 minutes. In contrast, only Zaleplon 20 mg was better than placebo. For number of awakenings there were mixed results and one drug did not appear better than the other using the indirect comparisons of placebo.

Next slide. This shows the fourth head-to-head study of Zolpidem versus Zaleplon. It was a single dose study where they looked at patient's preference. And after a single dose more patients preferred Zolpidem, but the difference was not statistically significant. There were only 53 patients in this study. From the UK meta analysis they found that patients taking Zaleplon had less improvement in sleep quality with an odds ratio of 0.66.

The next slide shows results for rebound insomnia. Zolpidem caused more rebound sleep latency than Zaleplon in the three head-to-head studies and there was a rebound decrease in sleep duration with Zolpidem but not with Zaleplon. In adults the rebound increase and the number of awakenings…there was a rebound increase in number of awakenings with Zolpidem but not Zaleplon, however, there was no rebound increase in number of awakenings in older adults with either drug. So in non-elderly patients Zolpidem was worse than Zaleplon for rebounds. And the difference in the one head-to-head trial in which we were able to calculate the risk difference ranged from 34 to 41 minutes for different doses favoring Zaleplon for rebound sleep latency.

The next slide, slide 12. This shows there was no difference in overall adverse events or withdrawals due to adverse events in any comparison of Zaleplon versus Zolpidem. I think in this slide, the version that you have, the first column of this slide is not correct. It just shows the same Zaleplon 5 mg versus Zolpidem 10 mg. The numbers are correct, but the doses should be different for the other rows. So the point is that no

matter what the dose comparison was there was no significant difference in adverse events. You can find the correct table in our report in Table 6, on page 16.

Okay. So the next slide shows our summary of results for Zolpidem versus Zaleplon and the quality of the overall body of evidence is good. Each drug had advantages depending on the outcome measure. There's evidence that Zaleplon was more effective than Zolpidem for sleep latency, but Zolpidem was more effective than Zaleplon for sleep duration and sleep quality. The drugs were similar for the number of awakenings and for daytime alertness. Zolpidem caused more rebound insomnia on the first night after discontinuation, but short-term adverse advents and withdrawals due to adverse events were similar.

The next slide. The next three slides concern the comparison of Zolpidem to Zopiclone, the Canadian drug. So I'll just quickly summarize what we found, which was that the drugs were similar on patient rate of sleep outcomes and on physicians global assessment of improvement. But Zopiclone caused more rebound sleep latency. Overall, adverse events and withdrawals due to adverse events were similar in one study that measured the effective withdrawals as a primary outcome. So we can skip now to slide 17, which shows the comparison of Zolpidem versus Eszopiclone. There is one head-to-head trial. It's not fully published, but it is published as a poster and we found additional information from the FDA review and from information submitted by the funder of the study, which was the maker of the Eszopiclone.

In this head-to-head study the primary efficacy outcome was objective sleep latency measured by PSG over two nights. The results showed a slightly shorter sleep latency for Zolpidem 1 mg than Eszopiclone 1 mg. The mean difference was 8.6 minutes with a confidence interval of 1.68 to 15.5 minutes. There was no difference between Eszopiclone 2 mg or 3 mg and Zolpidem 10 mg. Sorry, the slide is wrong where it says Zolpidem 1 mg. It should be 10 mg. And there was no difference in objective wake time after sleep onset, which is measured in the sleep lab with a PSG. And next day effects were similar including morning sleepiness, daytime alertness and daytime ability to function.

The next slide shows indirect comparisons of Zolpidem versus Eszopiclone that we made from placebo-controlled trials. Since we only had the one head-to-head trial we also looked at placebo trials. We found that there is evidence that the drugs were similar for sleep latency and number of awakenings, but Eszopiclone was more effective for increasing sleep duration. But the comparisons were limited due to differences in populations across the placebo-controlled studies. And the quality of the overall body of evidence is fair.

The next slide shows the comparison of Zaleplon to Eszopiclone and there were no head-to-head trials. Limited indirect evidence from placebo-controlled trials suggests they are similar for sleep latency at one week. We were unable to look at other sleep outcomes due to limited information.

The next slide is Zaleplon versus Zopiclone, the Canadian drug. Again, no head-to-head trials and limited indirect comparisons suggest that they are similar for sleep latency at one week. The quality of the overall body of evidence was poor.

The next slide, slide 21, shows a table showing a summary of the comparative evidence for short-term efficacy. So you can see that the different drugs had advantages or disadvantages based on which comparison…or which outcome was used. And there's no slide for it, but I just wanted to summarize the results of our comparison…our results of our review of the active control trials. First, Benzodiazepine – there are no studies of Zopiclone versus Benzodiazepine. For the other newer sedative hypnotics most comparisons found the newer drugs to be similar to Benzodiazepine in efficacy and short-term adverse events, but some studies did find less rebound insomnia with the newer sedative hypnotics. And then we identified one fair quality short-term trial of Zolpidem versus Trazodone. A second trial was conducted in elderly patients and it was rated poor quality so we didn't use it for the overall body of…assessing the overall body of evidence.

In the fair quality trial sleep latency was shorter with Zolpidem after one week of treatment, but the difference was not significant at week two compared to Trazodone. Sleep duration, number of awakenings, sleep quality, and patient's global impressions of treatment were similar for Trazodone and Zolpidem at weeks one and two, but more patients reported day time somnolence with the Trazodone. Withdrawals due to adverse events and overall adverse events were similar for the two drugs.

The next slide – comparative long-term efficacy. There is no evidence about comparative long-term efficacy. There is a six-month placebo controlled trial of Eszopiclone 3 mg and Eszopiclone was better than placebo for the outcome sleep latency, sleep duration, number of awakenings, sleep quality and daytime alertness. But rebound insomnia was not assessed in this study.

The next slide. This is other evidence about long-term safety. Again, there is no comparative evidence and the evidence is limited. Flurazepam we identified one-year open label extension study in elderly patients. This was a highly selected population – patients who are able to tolerate the drug for I think it was six months. In this study 64% of patients completed 12 months of treatment. The most frequent adverse events were headache and infection and the most frequent adverse events results in discontinuation were pain, [inaudible] or dizziness and GI disturbances. There was a significant increase in rebound sleep latency, number of awakenings and reduced total time slept on the first night after discontinuation after taking the drug for a year. And Flurazepam we found two open label studies that [inaudible] over six months. In six months, 7.3% of patients withdrew due to adverse events that were considered related to the drugs. Some of these were a feeling of strangeness, a feeling of drunkenness, amnesia, nausea, confusion and two patients experienced nightmares, but not considered related to the study drug. There were no reports of withdrawal or rebound phenomena with Zolpidem.

The next slide. Continuing long-term safety. In the six-month placebo-controlled trial of Eszopiclone that we discussed under efficacy overall adverse events were 81% for Eszopiclone and about 71% for placebo. The most common was unpleasant taste and

more patients discontinued due to adverse events. In the Eszopiclone group 12.8% versus 7.1% for placebo. Following discontinuation there were similar rates of adverse events for placebo and Eszopiclone, about 11% in both groups.

The next slide. Evidence for subgroups. First, older adults. The two-week trial, the head-to-head trial of Zaleplon versus Zolpidem in older patients that we discussed earlier found that efficacy was similar to that in younger adults. Daytime somnolence was more common with Zolpidem than with placebo or with Zaleplon 5 mg. But there was no difference in overall adverse events or withdrawals due to adverse events. We also identified a case controlled study of the relationship of the use of Zolpidem in hip fracture in over 6,000 elderly women. There was an increase to risk in patients using Zolpidem with an adjusted odds ratio of 1.95 and this was higher than the risk for Benzodiazepine, which was an odds ratio of 1.46. So both Benzodiazepine and Zolpidem found the higher risk of hip fracture. And then we didn't find any other similar drugs…similar [inaudible] than the other newer sedative hypnotics about hip fracture.

The next slide. Subgroup based on gender or race ethnicity. We found no evidence that once newer sedative hypnotic is safer or more effective for any subgroup. The studies just did not report sub analysis based on these characteristics.

The next slide – Use in pregnancy. We identified one prospective cohort study of Zopiclone, which was conducted in Canada with 40 women who had contacted a counseling service. They had taken Zopiclone in the first trimester of pregnancy and they found that Zopiclone was associated with a lower mean birth weight and gestational age, but no differences in the outcomes of pregnancy.

The next slide. Patients with subgroups based on patients with co-morbid conditions. We found no direct comparative evidence in child versus Benzodiazepine we found for Zopiclone with similar efficacy and adverse events in patients withdrawing from alcohol, patients with anxiety, and in patients with stroke. Zolpidem 5 mg, but not 10 mg was more effective than Triazolam for sleep outcomes in patients with COPD. And from placebo-controlled trials we found evidence of efficacy for Zolpidem in patients with depression and other psychiatric conditions and in patients with fibromyalgia. Prazepam efficacy better than placebo in patients who are having kidney dialysis and the important point here is that the studies don't provide evidence about comparative efficacy in these sub groups. And that concludes the presentation. Thank you.

Daniel Lessler, MD: Susan, can you hear me?

Susan Carson, MPH: Yes.

Daniel Lessler, MD: Okay. Can you hear me now?

Susan Carson, MPH: Yes.

Woman: This is through a microphone. Can you hear me?

Daniel Lessler, MD: Am I sort of distant or…

Susan Carson, MPH: You're kind of distant and echoing. Now it sounds good.

Daniel Lessler, MD: Right. Okay, well, we're still having a little bit of a problem making it so that you can hear everybody here when they speak. So I think what we're going to do is…I'm actually talking on a cell phone and I think what we're going to do is I'll pass questions or receive questions for you. But before we do that we have a new member of the committee that I just wanted to introduce. Ken Wiscomb who is a physician's assistant, I believe, is joining the committee today. And Ken, welcome. Maybe you could tell people a little bit about yourself, where you're from and the nature of your practice.

Kenneth Wiscomb, PA-C: I live in Bellevue and Ravensdale. My practice is [inaudible].

Daniel Lessler, MD: Thanks. Well, welcome. Usually we don't have quite this degree of technical difficulty. Okay. So Susan what I was going to do first is I'm going to ask if any of the committee members had specific questions for you. So, actually what I might do is just pass the phone. So first is [inaudible].

Vyn Reese, MD: Hi. This is Dr. Reese.

Susan Carson, MPH: Hi.

Vyn Reese, MD: I wonder if you could comment on data on abuse and dependents with newer agents? And do you have any data on those concerns?

Susan Carson, MPH: Yeah, the only data that we found, the only evidence we found were individual case reports of abuse and dependence. We found that for…let me just look it up here. We found it for two of the drugs. No studies…no case reports of the ones that had been on the market for the least amount of time and our conclusion was that there is a possibility of abuse and dependents and for the newer drugs there might not have been enough…they might not have been around long enough for these reports to have come to life.

Vyn Reese, MD: So you do have reports on Zolpidem or…in some of the older drugs, but in the newer ones? Is that right?

Susan Carson, MPH: Right. Like not on Eszopiclone, yeah.

Vyn Reese, MD: Okay. Thank you.

Susan Carson, MPH: I want to make sure I tell you exactly which ones I…I'm looking it up in our report right now. Okay, so yeah, we found case reports for…with Zolpidem and Zopiclone were the only two, but not for Zaleplon and Eszopiclone.

Angelo Ballasiotes, Pharm D: This is Angelo Ballasiotes. I wonder if you have any information…I'm looking at your long-term safety information. It says here on Zaleplon 12 months of

treatment there was infection in 15% of the people in the studies. Can you comment on that? What were the infections?

Susan Carson, MPH: Um, I don't think the report said what…specifically what they were. I'm not sure if they were considered related to the study drug either. I think the way it was reported was just infection with no detail.

Angelo Ballasiotes, Pharm D: Thank you.

Daniel Lessler, MD: I think we have some more questions here for you, Susan.

Robert Bray, MD: This is Dr. Bray. On the hip fracture data you mentioned that the relative risk for Zolpidem was higher than the relative risk for [inaudible]. With that…was that the number of [inaudible] was that one particular one?

Susan Carson, MPH: Let's see. I think it was a combined—any Benzodiazepine.

Robert Bray, MD: And the follow up question is, was that from the same study group or were they taking a relative risk from a different population?

Susan Carson, MPH: It was the same population. It was a case-controlled study.

Robert Bray, MD: Thank you.

Daniel Lessler, MD: Is there any other questions for Susan from the P&T Committee members? Okay. I think at this point what we'll do is open up for stakeholder input. Susan, can you hold on for just a second here?

Susan Carson, MPH: Sure.

Daniel Lessler, MD: Susan, what we're going to do is we're going to…when stakeholders comment, we're actually going to give them the phone. So you'll hear them as well. First on the list that I have here is Dr. Robachinski and we ask if you could please identify whether or not you are representing any manufacturer or any such ties and also please limit your comments to 3 minutes. Thanks.

Chet Robachinski, MD: I'm Dr. Chet Robachinski, a psychiatrist in private practice. I am the founding partner of Associates and Behavioral [inaudible] and I am the Psychiatric Director of the Bailey Boushay House, a facility who serves people with AIDS. I'm on the Speakers Bureau for…

Daniel Lessler, MD: Excuse me, doctor. We're having a little bit of trouble hearing you.

Man: I think it would be best if you spoke into the microphone because we're trying to take a transcript and hopefully she will be able to hear over the cell phone. Maybe you need to be addressing to the committee.

Chet Robachinski, MD: So I should start over again?

Daniel Lessler, MD: Yeah, please.

Chet Robachinski, MD: Hi, I'm Chet Robachinski, psychiatrist in private practice in Seattle. I'm one of the founding partners of Associates and Behavioral Health and I'm the Psychiatric Director of Bailey Boushay House, a facility who serves people with AIDS, 99% of whom have Medicaid for insurance. I'm on the Speakers Bureau for Wyatt, Glaxo Smith Klein and Pfizer. I'm here today to present the clinical rational for the utilization of non-Benzodiazepine sedatives in the management of chronic insomnia among psychiatric patients. I believe that the best way to demonstrate the importance of including these agents as options for treatments is to discuss clinical cases. The first person I would like to discuss is attends the adult day health program at the Bailey Boushay House. He is a 38-year-old gentlemen diagnosed with major depression since his early 20's who has been disabled for over 10 years with AIDS and depression. He has suffered from chronic insomnia characterized by both initial difficulty falling asleep as well as mid cycle awakening for at least the past six years. Perhaps secondary to his HIV medications, the pain he endures from HIV-related neuropathy or his depression. He has had multiple trials with adequate doses and duration of treatment of all of the agents commonly used to treat insomnia including Amitriptyline, Trazodone, [inaudible], Flurazepam and Temazepam. These agents have either stopped working for him due to tolerance occurring or led him to have severe daytime somnolence. Left untreated his lack of sleep results in a worsening of his neuropathy pain and a worsening of his depression. He was prescribed Eszopiclone 3 mg soon after its approval and in his words considered it a "miracle drug" and that he had excellent quality of sleep for 7 to 8 hours with no residual somnolence the next day. Unfortunately, he was only able to receive this treatment 10 days a month despite the fact that his insomnia occurs nightly without it. As his prescriber it is a very frustrating feeling for me to have finally found a medication that works for his symptoms only to be thwarted by his insurance, which will only cover 10 pills of Lunesta a month despite the fact that it is approved by the FDA for long-term use. I should also state that an authorization for an exception to this 10-pill rule was denied by Medicaid.

The next case I wanted to discuss contrasts how those with private insurance can actually receive the treatment they need to allow for adequate control of their insomnia and thereby better control of their psychiatric symptoms. This is a 48-year-old woman with bridle bipolar disorder whose effective symptoms are exacerbated by her chronic insomnia. Suffice it to say that after the usual trials of sedatives she is now taking 6 mg of Lunesta along with 12.5 mg of Ambien CR every night with excellent control of her insomnia and no residual daytime effect nor signs of tolerance after four months of treatment thus far. Her bipolar symptoms are under control for the first time in seven years and she's able to function on her job again. In conclusion, I would like to say that I could go on for three hours as opposed to three minutes discussing similar cases, but the vital message I wanted to convey is that in the best interest of our patients, Washington Medicaid should follow Oregon's lead and allow at least one of these agents to be approved for 34 doses a month without the prior authorization requirement. Thank you for your time.

Daniel Lessler, MD: Thank you. Are there any questions for Dr. Robachinski? Okay. Thank you. Can we just check…Susan might not be able to hear us at this point, but…

Woman: Could you hear that, Susan?

Susan Carson, MPH: Yeah, I couldn't hear any of that, I'm sorry. If there is a question for me could it be repeated, please?

Daniel Lessler, MD: I think if she can just stay on the line and then she won't be able to hear, but if there are questions because sometimes there are points of information that come up from committee members and it is useful to have Oregon on the line. So if…we apologize that you can't hear us, but if you could just stay on the line. We probably have another 12 or 15 minutes of comment and then we can wrap this up.

Susan Carson, MPH: Okay.

Daniel Lessler, MD: Okay. Thanks.

Susan Carson, MPH: So there were no questions from the last speaker?

Daniel Lessler, MD: Next is Dr. Hellekson.

Carla Hellekson, MD: Good morning. I'm Carla Hellekson, a psychiatrist and also board certified in sleep medicine. Insomnia has been my particular area of interest throughout my career. I should disclose that I am on the Speakers Bureau for Glaxo Smith Klein, as well as [inaudible] Pharmaceutical. I come to you today as a community psychiatrist at Valley City Counseling and Consultation where my case load, a very complex, chronically mentally ill patients is estimated to be 66% Medicaid and 16% Medicaid plus Medicare. I urge you today to consider to allow 30 tablets in 30 days of one of the new BZRA's, Benzodiazepine Receptor Agonist such as Zopiclone. I understand the origin of the 10 tablets in 30 days. I was actually at the insomnia conference in the 1980's where we came up this recommendation, but that was the days of Flurazepam with its very long half life, as well as the long half life of its active [inaudible] and this is a new age. What was missed in the lovely literature review since it went through May 2005 I heard her say this morning is the excellent state of the Science Conference that was done at NIH June 13th and 15th, 2005 on chronic insomnia and it was published in our journal of clinical sleep medicine and it is also available on line and I urge you to look at it. May I quote from it? One of the 8 FDA approved medications for insomnia…of the 8 FDA approved medications for insomnia only one of these medications Eszopiclone has been approved for use without a specific time lime. The others are limited to 35 days or less. This is because of the crystal study and in your packet from OHSU that is reference number 75 and in the PowerPoint slides today it looks to me like she got the data for slides 22 and 24 from that study. The state of the art paper also looks at the limited evidence for the efficacy of the off label medications used to treat insomnia. We know these have multiple major side effects—Trazodone, with the side effect of priapism and I'm increasingly concerned by the use of [inaudible], as a sleeper. This is an expensive, up to $7.00 a tablet choice with a myriad of side effects. My clinical experience with patients who are on nightly [inaudible] at 3 mg is that they have improved day time effectiveness and the … (inaudible) is the BZRA with the best evidence-based effectiveness for nightly use and

is the cost-effective agent in working with patients with insomnia and co-occurring mental and medical disorders. Thank you very much.

Daniel Lessler, MD: Thank you. Any questions or comments? Okay. Next is Michael Herman.

Michael Herman: Hello. Thank you for the opportunity to speak today. My name is Mike Herman and I work in the Medical Affairs Division of Sepracor as a CNS Medical Liaison. Today I would like to read a few brief statements on sleep and insomnia and share the highlights of the data supporting the use of Lunesta or Eszopiclone in the treatment of insomnia. Lunesta's parent compound, Racemic Eszopiclone has been marketed around the world [inaudible] since 1987. It is the most prescribed…it is one of the most prescribed hypnotics outside the U.S. with over 22 million patient years of experience. The goal of Lunesta clinical development program was to develop a lower dose versus Eszopiclone that would achieve rapid sleep onset and maintenance with no next day residual effects in most patients. Lunesta or Eszopiclone is [inaudible] of [inaudible] and possesses nearly all the pharmacologic activity. Lunesta has been proven to decrease sleep latency and increase sleep maintenance. Lunesta has been studied in clinical trials in over 6,000 adults with studies ranging from one night to 12 months across a wide spectrum of insomnia types including elderly and non-elderly adults, transient and chronic insomnia, primary insomnia and coexisting insomnia including depression, general anxiety disorder, menopause, rheumatoid arthritis and [inaudible] sleep apnea.

[inaudible] six phase three pivotal studies to the FDA for approval. These studies used both objective polysomnography and subjective patient self reports. Both accepted and validated measures of collecting efficacy data. Phase 3 clinical studies range in duration from one night to six months double blind placebo control with one study continuing for an additional six months as an open label trial for a total of 12 months of data. I would like to correct the statement in one of the slides that was shown earlier of a head-to-head study of Eszopiclone versus Zolpidem. It was not a head-to-head study. It was actually a comparative trial versus placebo. The question I would like to answer for you today is if you were to just choose one agent for your preferred drug list [inaudible] it should be Eszopiclone. Insomnia symptoms range from difficulty falling asleep to awakening throughout the night. The problems with awakening too early or experience in [inaudible] and next day functioning. Studies have demonstrated that the majority of patients experience two or more of these symptoms in insomnia. These symptoms may change over time. With the addition of Lunesta and medication with proven efficacy in treatment all of these various symptoms there will be no need to incur additional resources to switch medications based upon the presenting and changing insomnia symptoms. Lunesta is the first and only hypnotic with proven long term safety and efficacy in clinical trials. In fact, as mentioned earlier Lunesta was the only non-Benzodiazepine to receive acknowledgement from the latest NIH State of the Science consensus statement on the treatment of insomnia in adults. The NIH panel provides a guideline created by sleep experts based on [inaudible] validated double-blinded gold standard research studies to provide a roadmap for physicians for insomnia. The NIH did not support the use of over-the-counter sleep aids, anti depressants or atypical anti psychotics for the treatment of insomnia.

Long term safety and efficacy data for Lunesta is the result of a landmark multi-center U.S. based Phase 3 study conducted by Dr. Crystal and colleagues. The study was a randomized double blind placebo-controlled nightly dose trial of the [inaudible] versus placebo over six months with an additional six month open label extension phase. This study was published in the Journal of Sleep in November 2003 and as a result of this long term study and several other high level evidence studies Lunesta is approved to treat both short term and chronic insomnia, its approved for both sleep onset and sleep maintenance insomnia symptoms. It's the only hypnotic agent proven to demonstrate a lack of tolerance, [inaudible], rebound or significant next day effects in double blind placebo controlled trials for six months with continuous use.

Daniel Lessler, MD: I'm going to have to ask you to wrap it up here if you would.

Michael Herman: [inaudible] separate Lunesta from the currently available [inaudible]. So in conclusion Lunesta is indicated to improve…improvement to improve sleep both short term and long term for difficult…falling asleep and staying asleep through the night. It's the only hypnotic with proven and demonstrated efficacy in nightly, six-month double blind trials [inaudible] patients not only having problems falling asleep, but staying asleep and Lunesta provides 70% of the patients 7 to 8 hours of sleep each night. Thank you.

Daniel Lessler, MD: Thank you. Any questions or comments?

Woman: I'm trying to test this line really quick. Susan, are you there?

Susan Carson, MPH: I'm here and I can hear you.

Woman: You can hear me, but you can't hear anyone else?

Susan Carson, MPH: Not really.

Woman: I'm going to try recalling the phone in here to see if we can get this to work. Bear with me, okay. Don't hang up, Susan.

Susan Carson, MPH: Okay.

Daniel Lessler, MD: I apologize. Next is Jon Sonoda.

Jon Sonoda: Hi. My name is Jon Sonoda. I'm a regional medical science manager for Sanofi-Aventis. Basically, a couple of things, you know, that NIH can sense a statement to the FDA. It discussed a few things and what they are saying now [inaudible] is that all sleep medications are probably going to be used on a more chronic basis. This is something that has changed recently in the FDA's view on all non [inaudible]. I think it's also important, and unfortunately we don't have too much data on Ambien CR today, but this is the product I want to discuss with you. Ambien CR is actually very unique in nature. It actually has a fine [inaudible] characteristic. So most of the drug is actually released up front to reduce [inaudible]. The rest of the medication is released slowly over the next four hours to increase sleep maintenance. I think it's

important for you to realize that Ambien CR actually mimics normal sleep human body [inaudible], which is important.

A few things as far as safety is concerned, you know, when you look at long term safety you want to talk about trial and physician usage. The truth is, you know, over the last 12 years Ambien has been the most widely prescribed sleep aid [inaudible] class. You have over 200 trials with 59,000 patients and over 12 billion patient nights of use. Over this time the drug had never showed any changes in cardiovascular [inaudible] damage. I think it's important that you realize that it hasn't been demonstrated as an [inaudible] potential or [inaudible] over the years. Finally, I want to [inaudible] some things as far as Ambien ER. It [inaudible] hypnotics and also the agency for health care quality and research. Just a couple of statements if you actually got a chance to look at that. It goes on and says that there is evidence that chronic insomnia is obviously associated in people with psychiatric illness and mental conditions, as well as increased health care utilization. Also in their main conclusion they said that there is evidence that Benzodiazepine have a greater risk of harm than non-Benzodiazepine. Ambien CR is actually fit [inaudible] what we call kind of an ideal sedative hypnotic with a very short cap life. [inaudible] onset and again a very long-term safety profile. For these reasons I think you should consider adding Ambien CR to your preferred drug list for the State of Washington. Thank you.

Daniel Lessler, MD: Thank you. Susan, can you hear us?

Susan Carson, MPH: I can hear you now.

Daniel Lessler, MD: Great. Next is Dr. Pascualy.

Ralph Pascualy: Good morning. I'm here today officially on invitation from the distributors of Sonata, but I consult, speak and run Phase 3 trials for everybody, whoever has made a drug for sleep. So just to let you know that. The point I wanted to make is I'm the director of the Swedish Sleep Medicine Institute and we have seven full-time providers there. [inaudible] 5,000 patients a year and my personal mission is to educate physicians on how to practice. So my viewpoint is a little different. I think the data is fair that these drugs are effective…the drugs that we are looking at today and I believe that it's important for all of them to approved for the simple reason that in order to provide care across a spectrum of patients, you need different medications with different properties. A good example is Sonata. You saw in the summary slide that Sonata is very effective to put people to sleep, not as effective though at keeping them asleep and sleep quality. This becomes very useful in a very significant problem. Many patients have trouble sleeping because they wake up in the middle of the night. What's happening now is that patients in fact are given the drug at bedtime, but at bedtime the patient doesn't know if that particular night they are going to wake up. So you end up with someone taking a pill every single night hoping that that particular night they won't wake up.

Sonata, the way I teach physicians to use it is give a drug that is safe in the middle of the night so that the patient takes it only the nights that they wake up and this way you don't end up with the chronic use. And that's a self-population. We can go ahead and take arguments on how to use Ambien in certain populations where Sonata isn't as

effective. Similarly, with the longer acting drugs. So my sense of it is that there is a lot of competition about trying to get a particular drug on this formulary. I think as well trained physician requires different tools to do the job and my hope is that you allow all of these medicines, which have different clinical benefits on board.

One last thing, I don't believe it's correct to say that sedative [inaudible] now being looked at as a chronic…for chronic use variables. For every chronic insomnia in the United States there are 10 who have intermittent insomnia who require treatment and therefore you have to have strategies that don't end up putting everybody on a prescription forever. And I think, again, that speaks to my thought which is if you're handling this area it would be very worthwhile to communicate to your prescribing physicians about appropriate use of these medications and to do more teaching because that's what is going to avoid the [inaudible] utilization or having patients on chronic medication. Thank you.

Daniel Lessler, MD: Thank you. Any questions, again? Susan, are you still there? No. Okay. And finally the last person I have is Dr. Larry Cohen.

Larry Cohen: Thank you for the opportunity to make a couple of statements. I'm Larry Cohen. I'm a professor and Chairman of the Department of Pharmacotherapy at Washington State University. I'm not here representing any pharmaceutical company or special interests. A couple of comments from the presentation that was made today. First, it's pretty clear as you look over the compounds that were presented half life is not the same as duration of effect. Hopefully that's something that members of the P&T picked up. If you look at, for example, I think it was Zaleplon with a one-hour half-life and Eszopiclone with a six-hour half-life if you look at the duration of effect of those compounds it's really not that amount of time. So duration of effect and half-life are two different issues.

I also wanted to make the point that sleep architecture changes as a consequence of using these drugs. These drugs are actually very useful for people that have chronic sleep disorders and can actually correct some of their problems and that beneficial effect seems to be sustained in many patients even after the drug stopped being used.

Next, having to do with Trazodone since the drug that is fairly commonly used out in the world, I don't believe it is FDA approved for treatment of sleep disorders though it is widely used in the community and the adverse events have already been discussed including the carrier of [inaudible] during the day and hypertension. Since I heard specifically data having to do with hip fractures from Benzodiazepines I want to point out that in a lot of studies of sleep drugs they look specifically at sway. It was looked at for all of the Benzodiazepines selective compounds that were presented today. These are highly selected compounds and don't behave like the traditional Benzodiazepines. I believe the risk associated with hip fractures is substantially greater with Trazodone, a drug that's been fairly widely used. And last I just wanted to state that based on safety and efficacy these agents should clearly replace the agents that are widely used and inexpensive. Specifically Amitriptyline, Trazodone, other anti-depressants and the A typical antipsychotics.

Daniel Lessler, MD: Thank you. Any questions, again? What we're going to do…we're scheduled, I believe, for a break at this point. Then we can come back and deliberate. So we're going to take a break and reconvene at 10:15.

We'll have an open discussion here and then gradually move our discussion towards a recommendation. Yeah?

Woman: Let's release the conference call operator if you're still on the line. I believe you can go now.

Daniel Lessler, MD: Conference call operator, are you there? No. So why don't we just hang up.

Woman: This is the conference call operator.

Daniel Lessler, MD: Thank you. We're done. We're going to end the call now. We just want to let you know we've finished up and are going to release the call here. Thank you.

Woman: You're welcome.

Daniel Lessler, MD: Great. So maybe we can just begin. I don't know if there is anybody who has any specific observations or comments on the material we've heard thus far. Please, identify yourself.

Vyn Reese, MD: This is Dr. Reese. Given our technical problems it wasn't clear if…it's pretty close. Can you hear me? I'm sort of thinking out loud and to me it looks like these agents are very heterogeneous. Some are better at sleep latency, others are better at sleep duration. Whether they are safer in the elder as far as hip fractures go, it doesn't look like maybe they are, which is sort of surprising and the only data that was presented to the committee doesn't look like they are safer, which is disturbing. There is also some risk of abuse in dependence, which we also already had with the Benzodiazepines. It's unclear to me where they fit. I think some patients probably clearly need to be on them. As we were told by Dr. Pascualy this is a very heterogeneous population—patients with insomnia. There are lots of different sub groups that need different drugs. So the question is, "Which drug do you add in that situation or do you just leave it for the provider to request a drug?" The other concern I have is for chronic insomnia I think probably the 10-day limit needs to be maybe for patients who have limited insomnia, but there needs to be some mechanism if you have chronic insomnia that you can get a drug for 30 days. That doesn't seem right that a provider can't call and explain the situation in a patient who has a chronic insomnia problem and clearly needs a drug that they can't get it for 30 days. So I think we probably need to change that policy. It should be 10 days for most people, but there is going to be occasional patients who need a longer course of treatment. I don't see adding any of these drugs to the Preferred Drug List at this point and leaving it up to providers to request them. That's sort of my take on it. I don't think they are that much safer than Benzodiazepines or that much more effective. There are subgroups of patients that that may be better in, and the doctors can figure out that patients and request the drug for them. That's my take on it. I would prefer not adding any of them—letting doctors choose the patients they want to prescribe them in and making sure there is an

avenue for a 30-day supply in a sub set of patients who really need that and who are going to be on these drugs long term. Thanks.

Daniel Lessler, MD: Thanks. Other comments? Angelo.

Angelo Ballasiotes, Pharm D: This is Angelo Ballasiotes. I guess I kind of echo that with regards to the 10-day limit. I deal with mental illness and also people that have a chronic sleep problem. And boy oh boy, I think we end up spending more money on using other drugs that might have an indication for sleep and getting to people to sleep and having them stay asleep. I don't know how that 10-day rule got in there. Maybe there is something that can be done to change it around for special patient groups.

Alvin Goo, Pharm D: Hi. It's Alvin. I agree that the data is sort of limited as far as really differentiating the benefits of one of these newer agents over another. In the future, though, I think we might revisit and possibly select one for PDL once Zolpidem becomes generic. I would agree with Dr. Reese.

Daniel Lessler, MD: I had a question actually. I think we tend to focus on the Medicaid formula, but actually our decisions potentially effect other formularies, as well. So my question is for example with respect to L&I and then particularly uniform medical is if there is not a recommendation with respect to place, you know, anything that would allow placing these on the PDL. How does that effect uniform medical? Does that automatically mean a medicine is…does that effect the tiering of the medicines and what somebody needs to pay? Because that wouldn't be the case with Medicaid where somebody could, a physician could call or whoever could call, I mean in terms of what we're talking about here. They might be able to call and get authorization based on clinical circumstances and we can talk about making that sort of administratively efficient and so forth and allow for a 30-day supplies. But I'm concerned about the other formularies in terms of how the decision-making might impact…

Donna Marshall, Pharm D: This is Donna Marshall. I'm not quite sure I understand. Are you saying that you might be recommending not adding this whole class to the PDL or just one particular drug?

Man: The class.

Donna Marshall, Pharm D: Then we would continue with our current status right now that they are based on the express Scripts formulary. So the tiers would remain the same. Whatever they are today I don't know off the top of my head, but whatever they are today they would remain that.

Daniel Lessler, MD: And just to clarify so we understand implications and decisions. If, for example, we specified that one medicine in this class should be…or a medicine from this class should be on the PDL how does that impact the Uniform Medical in terms of its formula?

Donna Marshall, Pharm D: Well, if one of them should be on the PDL then you're putting the class on them. So all of the others, if they are not PDL drugs, would be tier 3.

Daniel Lessler, MD: And if the one that is PDL would that put it in a different tier?

Donna Marshall, Pharm D: It depends on if it's a different tier than it already is. Karen, do you know? So right now our preferred product is Ambien. So if one of the other drugs was named as the preferred drug then they would move from tier 3 to tier 2.

Daniel Lessler, MD: Okay. Thanks. And again, for L&I as well just so we fully understand.

Jaymie Mai, Pharm D: This is Jaymie Mai from L&I and if the whole class was not placed on the Preferred Drug List, same as Donna, we currently have [inaudible] agent then it will remain the same.

Daniel Lessler, MD: I guess the question I would…in just thinking about…and Angelo your comments…and just thinking those through. If the intent is…well, one concern I might have if this class is not on the PDL would be that people would preferentially perhaps prescribe less…potentially less effective or safe medications although I appreciate your comment that there is not a lot of data that we've been presented here that convinces you that what we're looking at is a lot safer than those that somebody else might currently prescribe merely because it's easier to access if you don't need to make a call or something in terms of the Medicaid formulary. So I would just put that out there as a comment for maybe people to react to. Patti, I see you…do you have a…

Patti Varley, ARNP: This is Patti Varley and I'm struggling here with my mission. Maybe you guys can all help me with this. And that is that if I am considering the evidence for safety, efficacy and special populations for the treatment of insomnia regarding these agents, including based on the limited data made available to me. I have to say that between these drugs in this class I cannot pick one as being safer or more efficacious. I could say that they have some evidence of different efficacy for different types of insomnia problems, but overall I couldn't say that. So my struggle here is, is my mission to say whether doing that review am I to say whether they as a class are on or not on the Preferred Drug List?

Daniel Lessler, MD: So your question is are we to narrowly make a recommendation based on sort of the framework that is up there or can we defer a recommendation? My sense is historically and in terms of precedent we have said that we can just, you know, remain moot and make no recommendation one way or another. And I will look at Jeff and make sure we're interpreting correctly here.

Jeff Graham, MD: This is Jeff Graham. We did make that decision on the A2RA's. We didn't think they should be first line drugs and they should not be included in our preferred drug list. Each agency would continue as they are presently operating.

Daniel Lessler, MD: Although, again, I would want to come back to the concerns that have been expressed around availability and supply and so forth with a 30-day supply as indicated.

Jeff Graham, MD: And I think that's probably sort of a DUR function in that I think if that was brought forward to…particularly HRSA that that would be something that this committee

would direct toward them and ask them to bring it back as a DUR function, which sounds like it is a concern. Right?

Daniel Lessler, MD: So Patti, it does sound like there is precedent there if that answers your specific question. Are there other comments with respect to these agents?

Alvin Goo, Pharm D: If we don't place this class on a PDL therefore does that mean that we will not be reviewed in another, you know, on course every…I forgot, six months?

Daniel Lessler, MD: It will be reviewed by the EPC because there are 17 clients that they have on this project that we have. So it will be reviewed and I think…this might be a fast track. I'm not certain about that, but they have already started the key questions for the second review. So I mean we could bring it forward again.

Vyn Reese, MD: This is Dr. Reese. That's what I'd like to do is bring it forward again at a later date. I don't think at this time we can choose between these agents as putting one of them on the PDL ahead of the others and I would prefer waiting and bringing it up at a later and leaving it the way it is except looking at the DUR function perhaps later in the day.

Siri Childs, Pharm D: This is Siri Childs speaking for HRSA and I just wanted to let you all know that we do have a set of criteria to look at chronic use and we do approve it given medical justification right now. It's just like any other drug situation given the right set of criteria we will approve it. We have that ongoing right now. I really support your recommendation because we have at least one new drug that is coming out or is out already that missed this review and it would be real important, I think, to cycle this again and study the new drug in comparison to these.

Jeff Graham, MD: This is Jeff Graham, again. I think since HERSA has some guidelines for approving more than the 10 that that is why this probably should be done at a time when you can see all that information.

Daniel Lessler, MD: You know, the one concern I have, Siri, and I'm actually thinking of Carol who is not here because I know wearing her hat she would be expressing concern about just probably having tried to maybe get a hold of one of these newer sedative hypnotics through MAA and having run into problems and so forth. I guess some of the stakeholders today commented on difficulty. I just would want to assure that, you know, that there is a process and it sounds like there is. Maybe, you know, letting people know what the guidelines are around being able to access extended…longer than 10 days, 30 days on an ongoing basis where it's indicated and so forth. Again, it is a good class of medicines when we are wearing our other hat as the, you know, DUEC to take a look at.

Nicole Nguyen, Pharm D: This is Nicole. I just wanted to clarify that with this class right now without requiring PA you can get the PEM for 30 as you know. To get more than that it will require the pharmacy to call and ask for prior authorization. Just to let you know, some of the questions we ask is we want to know the diagnosis, we want to know whether it is primary or secondary insomnia, what the underlying diagnosis is, are they treating that underlying diagnosis and how? What other measures have they done to

try to manage the insomnia such as non-drug and, you know, questions like that to run through. I know that there are some circumstances, especially mental health where they are doing everything…they are to try to treat underlying diagnosis and there is a…and we ask about functional impairment, as well. There is an actual daytime functional impairment that is evident.

Duane Thurman: Dr. Lessler, this is Duane Thurman. The committee might want to consider simply…and what it sounds like you're trying to get toward is that you're going to delay your decision pending the updated review.

Daniel Lessler, MD: I think that's where we're headed. Personally, I just wanted to get some clarification around the implications of doing that. So are there any other comments at this point? If not, I'm wondering if there is a motion. Actually, I would prefer…

Vyn Reese, MD: I move this be tabled and looked at again at a later date. This is Dr. Reese.

Daniel Lessler, MD: So there is the motion on the table to table this decision and it's been seconded. Is there any other discussion? Okay. All those in favor say, "I."

Group: I, I, I.

Daniel Lessler, MD: Oppose, same sign. All right. So we will table this until the next review. Thanks. All right then. The next item is…

Man: Excuse me. Is our line open now that he can call in?

Man: Dan, this is Gerald Gartlehner from the University of North Carolina and he's here to present the drug class review on target immune modulators. Do we have the slide up, Gerald? So you're free to start your presentation and then we'll have questions at the end for you. Can you hear all this or not? You're not hearing any of it?

Man: Can you hear us?

Daniel Lessler, MD: Dr. Gartlehner, can you hear me now?

Gerald Gartlehner, MD: You are fading in and out.

Daniel Lessler, MD: Can you hear me now?

Gerald Gartlehner, MD: I can hear you name.

Daniel Lessler, MD: This is Dan Lessler, I'm the chair of the committee. We have your presentation all lined up and the title slide is up. We can hear you just fine. So you can go ahead and get started with your presentation. Just let us know when you want to change the slide. Again, your title slide is what's showing now.

Gerald Gartlehner, MD: Well then, I'll get started. Welcome, again. My name is Gerald Gartlehner. I'm from the University of North Carolina and I'll be presenting our systematic reviews on targeted immune modulators today. If you look at slide two, for this

review we included six medications and they are listed on slide two as a [inaudible] and the other refused drug vary in their specific mechanisms of action and in the full reports we provide a complete summary of drug specific properties, including half lives and the dosing frequencies. Slide three, our populations of interest were pediatric patients with juvenile rheumatoid arthritis and adult patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn's disease.

Slide four…slide four lists the outcomes of interest and as always for these reviews for efficacy and effectiveness we have focused on [inaudible] such as functional capacity, quality of life and we reviewed intermediate outcomes if we could not find any evidence on health outcome. These outcomes were [inaudible] a variety of different scales and in the appendix of our report you can find descriptions of the most common scales like the ATR scale.

Slide five. For tolerability and safety we assessed overall adversity, discontinuation rates because of adversity, and then also rare but severe adversity such as serious infection, lymphoma, other immunity or congestive heart failure.

Slide six summarizes…included study design. As were previously reviewed we viewed head-to-head trials is the best evidence and if we could not find head-to-head trials we included placebo-controlled trials to assess the general efficacy of the drug. New for this report on targeted immune modulators is for effectiveness we have also included so called real world observational studies and those are observational studies that might have a greater [inaudible] ability than the efficacy trials. And in our analysis we tried to put the [inaudible] operational studies into context with the results from the efficacy trials. We limited the observational studies to those with at least one [inaudible] and minimal sample sizes of 100 participants.

Slide seven. Before I start with the findings of our review I would like to point out some special considerations for this drug class. Because rheumatic diseases are progressive in nature we limit the studies with the follow up of 12 weeks or longer. However, if we could not find adequate evidence then we took [inaudible] best evidence approach and we are still presenting the best available evidence. So even if they are shorter than 12 weeks. And because there was a lack of head-to-head trials for this drug class we conducted so called adjusted indirect comparisons and we described the pros and cons of this approach in much detail in the report and adjusted in the right comparison basically is a statistical method to indirectly compare drugs with drugs that have the same comparison groups. So in our case we looked at placebo controlled trials and so what we did was is we determined statistically where the one drug shows there is substantially greater effect compared to placebo than another drug. Adjusted indirect comparisons are subject to greater [inaudible] than direct head-to-head comparisons, but they can provide valuable information when direct comparisons are missing. They definitely have limitations and these limitations must be kept in mind.

Slide eight. Slide eight provides you with an… (inaudible) …comparing Etanercept to Infliximab for the treatment of rheumatoid arthritis. The large majority were placebo controlled trials excepting the general advocacy of part of the new modulated. As mentioned before, the five real world observational studies.

Slide nine, we did not find any evidence on Alefacept and Efalizumab; drugs are proved for psoriasis and apparently are not used for any other indications.

Slide ten, for rheumatoid arthritis we found one comparative effectiveness study. This was a Swedish, non-randomized, open label trial comparing Etanercept to Infliximab for the treatment of rheumatoid arthritis. Etanercept had a faster onset of action during the first six months but then at one year, no differences in response rates between the two drugs consisted anymore. This was…the only answer we had evidence that we found and the study design is prone to bias and confounding and results should be interpreted cautiously.

Slide 11, as I mentioned before, because we did not find any further direct head to head evidence, we conducted adjusted indirect comparison. Overall results of these indirect comparisons for rheumatoid arthritis indicates that no substantial differences in advocacy exists among the so called anti-TNF drugs, anti-tumor necrosis [inaudible] drugs. Those are Adalimumab, Etanercept and Infliximab. However, indirect comparison of individual anti-TNF drugs to Anakinra indicate that they are more efficacious than Anakinra

Slide 12 and slide 13 illustrate the results of these adjusted indirect comparisons of the anti-TNF drugs compared to Anakinra and to quickly summarize how these so-called forest blocks should be interpreted, what we did and what we have here are so-called relative risk forest blocks. The vertical axis in the middle represents a relative risk of one which means no differences in treatment effects. The black squares are the point estimates of the individual comparisons and the size of the square is determined by the size of the study population. The horizontal lines are the confidence intervals and if the horizontal line crosses the vertical line it's relative risk one, then this means that the difference is not statistically significant. Like if it does not cross, the difference then is statistically significant. In our case, everything to the right of the vertical line would favor Anakinra and everything to the left would favor the comparative drug. We did these indirect comparisons on ACR20 and ACR50 responses and outcomes and ACR20 response represented at 20% improvement of symptoms and likewise an ACR50 resembles a 50% improvement of symptoms. And ACR50 is usually…is a clinically significant improvement. As you can see in these forest blocks, the differences do not always reach statistical significance but they clearly favor Adalimumab, Etanercept and Infliximab over Anakinra.

Slide 14, other interesting findings from placebo controlled trials on rheumatoid arthritis were the targeted immune modulators are definitely highly effective treatments. We saw these results consistently across all trials. The combination with Methotrexate led to the best results for both patients with early rheumatoid arthritis as well as for patients with progressed rheumatoid arthritis. Three trials compared the efficacy of Etanercept to Methotrexate directly. That study end points no differences existed in health outcomes between Etanercept and Methotrexate. However the radiological progression was significantly less in Etanercept treated patients. One trial assessed the combination treatment of Etanercept and Anakinra. This trial did not find a synergistic effect and improved outcomes of the combination therapy. Adverse events, however, were significantly increased in patients who received the

combination treatment. In general, findings from observational studies from the real world observational studies were consistent with the efficacy trials.

Then slide 15, for ankylosing spondylitis, we did not find any direct comparative evidence. The placebo controlled evidence was insufficient for adjusted indirect comparison.

Slide 16, we found five trials for ankylosing spondylitis and these five trials provide good to fair evidence on the general efficacy of Etanercept and Infliximab for the treatment of ankylosing spondylitis. We could not find any studies on any of the other drugs.

Slide 17, similar to ankylosing spondylitis, no comparative evidence on targeted immune modulated exists for psoriatic arthritis and, again, the evidence was insufficient to conduct adjusted indirect comparisons for psoriatic arthritis.

Slide 18, we found only three trials for psoriatic arthritis and these trials provide evidence on the general efficacy of Etanercept and Infliximab and, again, we did not find any evidence on any of the other drugs for psoriatic arthritis.

Slide 19, for Crohn's disease the situation was similar. The evidence is limited to studies on the general efficacy. We could not find any head to head trials and, again, the evidence that we found was insufficient to conduct adjusted indirect comparisons.

Slide 20, with respect to the general efficacy, we found six randomized controlled trials and they provide fair to good evidence that Infliximab is efficacious for the treatment of Crohn's disease. Infliximab is efficacious both for acute as well as for maintenance therapy. Infliximab also proves efficacious for [inaudible] Crohn's disease.

Slide 21, by contract Etanercept did not show general efficacy for the treatment of Crohn's disease. This finding, however, is limited to a single trial. Again, no evidence could be found for any of the other drugs.

Slide 22, the evidence on juvenile rheumatoid arthritis is very limited. Not only did we not find any comparative evidence, the two studies on the general efficacy of Etanercept and Infliximab have [inaudible] limitations.

Slide 23, we found only one randomized control trial on Etanercept and this trial indicates general efficacy on Etanercept for the treatment of juvenile rheumatoid arthritis. The included population with highly selected and we were wondering if these results have any generalized ability to a broader population. The evidence on Infliximab was limited to one study with an extremely high attrition rate and basically this study must be considered fatally flawed.

Slide 24, key question two on slide 24 deals with the comparative tolerability and adverse events of targeted immune modulators and, again, the direct comparative evidence is limited to one open label head to head trial comparing Etanercept to Infliximab. Again, the [inaudible] study that I described before. Amongst trials, did

not detect any difference in adverse events. Overall full term tolerability of targeted immune modulators appears to be good and does not seem to differ substantially among drugs. Some differences exist, however, for example Anakinra appears to have a significantly higher rate of injection site reactions. Those are namely rash and itching. Infliximab which is administered intravenously can lead to severe infusion reactions in some cases. Most trials did not report any significant difference in adverse events compared to placebo. However, more importantly, the [inaudible] severe events are of equal concern for all targeted immune modulators.

Slide 25 summarizes the most important ones. Specifically these are serious infections, primarily tuberculosis, lymphoma, other immunity, congestive heart failure.

Slide 26, the existing evidence on this [inaudible] potentially fatal adverse events is severely limited by a lack of long term studies with inadequate sample size. Apparently the available evidence consists primarily of case reports and database reviews and adequately powered prospective studies are generally missing. We described the different severe adverse events in more detail in the report. At the moment it is very difficult to asses what the actual risks of these drugs are if the adverse events profiles among the drugs differ and if harms in some cases outweigh the benefits. For example, the package insert of Infliximab reports elevated liver enzymes in up to 30% of patients and some cases of liver failure are reports. But we could not find anything in the published literature on hepatic toxicity of Infliximab or if any other targeted immune modulators bears a similar risk of hepatic toxicity. Also some observational studies indicate that Infliximab might have higher risk of tuberculosis than Etanercept, but then again, this evidence is not very strong. It is basically limited to weak observational studies.

Slide 27, subgroups overall no controlled trials compared the efficacy of targeted immune modulators in a subgroup to the efficacy in the general population. For subgroups I will summarize the few studies that we identified.

On slide 28 H, full data from one study on ankylosing spondylitis indicated that there are greater benefits for younger patients than for older patients. However, this appeared to be a crude estimate and it can also be due to the fact of less structural damage has occurred in younger patients. No other studies on age could be found.

Slide 29, on sex, prospective core study reports that women develop antinuclear antibodies significantly more frequently than men when they were treated with Infliximab. Again, the clinical significance of this finding was very unclear.

Slide 30, three studies provided indirect evidence that Etanercept and Infliximab can worsen congestive heart failure. All three trials were conducted in populations with congestive heart failure but without any rheumatic diseases. The Etanercept studies had to be stopped early because of the higher mortality in the Etanercept group.

Slide 31, the evidence is insufficient to draw any firm effects of targeted immune modulators in patients taking other commonly prescribed drugs.

Slide 32, just to summarize our evidence. No double blinds, randomized trials compared targeted immune modulator to another. This is probably the main limitation of our body of evidence.

Slide 33, adjusted indirect comparisons such as the greater efficacy of Adalimumab, Etanercept and Infliximab than Anakinra for the treatment of rheumatoid arthritis. The evidence is insufficient to draw conclusions about the comparative effectiveness for all the other indications.

Slide 34, evidence is also insufficient to draw conclusions about the comparative safety and tolerability of targeted immune modulators. Rare but severe adverse events are definitely an issue for all targeted immune modulators.

In conclusion, slide 35, targeted immune modulators are definitely highly effective drugs for the treatment of rheumatoid arthritis and the other indications. Overall the risk benefit ratio, however, cannot be reliably assessed until long term studies with adequate sample sizes provides good evidence on the rare but severe adverse events. This is the second major limitation of this study of evidence is the lack of long term observational studies that are large enough to assess rare but severe adverse events. This slide ends my presentation. If you have any questions, please go ahead. I'd be happy to try to answer them.

Man: Thank you, Dr. Gartlehner. Actually, can you hear me?

Gerald Gartlehner, MD: Yes, I can hear you.

Man: Good. What we'd like to do now is open it up now to members of the committee to address questions to you. And then what we do after sort of that round of questioning and discussion is open it up to stakeholders in the audience that might want to comment as well, and if possible we'd like to ask you to stay on the line for that because sometimes that generates some additional queries on the part of the committee.

Man: Sure.

Man: Thank you. So, at this point I'm going to open it up to members of the committee to ask questions of Dr. Gartlehner.

Vyn Reese, MD: Hi, this is Dr. Reese. I had questions about risk of administration. And didn't really address that in your talk though it's in the body of the larger report that we had and reviewed. I guess that drugs that are administered intravenously do have a higher risk of drug related toxicity at the time of administration like Infliximab. Would you comment on that and about the seriousness of acute reactions to Infliximab?

Gerald Gartlehner, MD: I have acoustic problems. I think your question what are the risks of administration and if there is some association between the intravenous administration of Infliximab and hepatic toxicity? Was that the question?

Vyn Reese, MD: No, it's just acute reactions to Infliximab at the time of administration in addition to the hepatic toxicity to it which seems to be unique to that drug.

Gerald Gartlehner, MD: Okay. Well, there was one…evidence on one study that reported that in about 1% Infliximab can lead to sever infusion reactions. They are similar to severe allergic reactions. Nobody has died yet, but they think that the severe reactions…in about 10% there are infusion reactions that are less severe. Regarding the hepatic toxicity, the only evidence that we found was on the FDA web site and in the package insert. Otherwise, in the published literature there was nothing on hepatic toxicity and Infliximab. It was just surprising to us that it is in the package insert but nowhere else to find in the published literature.

Man: Thank you. Dr. Gartlehner, I had a question, maybe a clarification. In your conclusions, you make a general statement that all of the medicines are highly…just the [inaudible] are highly effective drugs for the treatment of multiple conditions. And yet in terms of what I would call reading and in your specific presentation you would speak to the fact that really with respect to some of these conditions, there is only evidence for Etanercept and Infliximab specifically with respect to ankylosing spondylitis and psoriatic arthritis and I think Infliximab with Crohn's disease. I wanted to just sort of clarify. It seemed to be a bit of a disconnect between that slide and the evidence.

Gerald Gartlehner, MD: Yeah, you are absolutely right. I probably generalized too much. This statement is limited to the evidence that we have on this specific drug. Except for Etanercept and for Crohn's disease for all the other studies that we have that are targeted immune modulators, these studies consistently showed a very large treatment effect. You are right; it is limited to these specific drugs and cannot be generalized

Man: Thank you. Other questions from the committee?

Man: I just had one other question. Plaque psoriasis was really not addressed in this review. Is that correct? And two drugs that are immune modulators, Raptiva and Amevive weren't mentioned because there was no data about them for the indications that were reviewed. Is that correct?

Gerald Gartlehner, MD: That is correct. We didn't find any data on them. Psoriasis was not one of our indications that we have.

Man: Any other questions from committee members before we open it up for stakeholders? Okay, Dr. Gartlehner, we're going to open it up now for stakeholder input and again, I appreciate you staying on the line to listen to this because sometimes there are additional questions that arise. I do have the list here. I want to remind stakeholders please if you could identify who you are and whether or not you have any ties to industry or have been sponsored to speak here today. And, as well, please limit your comments to three minutes. Appreciate that. First is Dr. Hurley.

Dr. Hurley: Hi. Thank you for the opportunity to speak today in support of Enbrel for addition to the PDL. I'm Dr. Dana Hurley, Health [inaudible] with Amgen. I received my PharmD as well as my masters in pharmaco economics from the University of

Washington. Prior to joining Amgen I was the specialty pharmacy program manager at Premera Blue Cross.

I'd like to take just a few minutes to highlight four key attributes of Etanercept and also provide some information on the [inaudible] PDL placement of this drug.

Each of the drugs for rheumatoid arthritis in your review really involved a different molecular structure as well as mechanism of action. That's outlined on page seven of the report. The impact of these differences highlights the first key attribute I will mention. In the report Etanercept is mentioned as a dimeric fusion protein, binds specifically to tumor necrosis factor alpha and beta and blocks its interaction with cell surface TNF receptors. This action is what differentiates Etanercept from the other drugs in production of antibodies. Etanercept is known only to produce non-neutralizing antibodies in 6% of patients as such neutralizing antibodies to the drug are not observed.

The second attribute of Etanercept is the breadth of indication. In table two on page eight of the report you notice that Etanercept has the broadest coverage. It covers both dermatology as well as rheumatology indications. Those are listed in there for you. Rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis and in pediatric patients for juvenile rheumatoid arthritis. But pediatric indication, perhaps as important to the Medicaid plan such as yours were the relative pediatric population may be large. Additionally, the depth of outcomes are proved by the FDA within these indications demonstrates improvement in physical function which may contribute to patients returning back to work.

The third attribute is the over 12 years of collected clinic trial experiences in over 308,000 patients worldwide across all indications, really afford the opportunity to fully evaluate the safety as well as the efficacy of this product. As reported by Clara Scott in 2005, the rates of serious adverse events and serious infections over the past seven years have remained low and are not significantly different from placebo or Methotrexate in clinical trials. Additionally, as mentioned in the report, there are no black box warnings for Etanercept. With regards to efficacy, Wineblack and colleagues have demonstrated the same efficacy with Etanercept in the treatment of rheumatoid arthritis over the past seven years.

The final attribute of Etanercept is in the dosing. As you can see in your review, the drug is administered as a 50 mg once weekly injection for rheumatoid arthritis. There is no labeling that allows for increasing that dose and it provides really a predictable dose as well as a predictable cost. This is uncharacteristic for these drugs in this class.

As mentioned I would like to share with you some important information on the PDL placement for Etanercept among other Medicaid plans. For all of the plans that have reviewed this drug, and there are about 30 of them or so, all of them have placed Etanercept on the preferred drug list and actually just two weeks ago Medical, which is the largest Medicaid plan, actually preferred Etanercept over the other products.

In conclusion, Etanercept does offer some unique advantages like the JRA indication, and predictable dosing, and it has a long term proven track record of safety and

efficacy in a number of indications, and respectfully requests Enbrel be added to the PDL. Thank you. Any questions?

Man: Thank you. Next is Dr. Nakanishi.

Dr. Nakanishi: Hi there, good morning. I am Marci Nakanishi. I'm a clinical executive in the clinical evidence and outcome group for Abbott Laboratories. I'm going to outline some of the strengths, or some of the clinical aspects or Humira or Adalimumab. As you probably know, Humira is the first fully human monoclonal antibody that is directed specifically towards TNF alpha. It binds with high affinity and specificity to both soluble as well as membrane bound TNF alpha and neutralizes its biologic function. Humira provides a rapid onset of action as seen in our DEO 2O study and our React study in which two-thirds of patients responded after just on dose as seen by the ACR20 scoring. It also significantly reduces signs and symptoms of rheumatoid arthritis within one week, improves physical function, and inhibits radiographic progression of disease as indicated by both joint erosion as well as joint space narrowing.

Humira is currently indicated for reducing signs and symptoms of rheumatoid arthritis, inhibiting the progression of structural damage, improving physical function with patients with moderate to severely active RA.

In 2005 we have gotten approval for two new indications, one of which is early rheumatoid arthritis and the second of which is psoriatic arthritis. That is an update from what you had seen in the slide presentation earlier. We also had two new publications. The first is our adept trial for psoriatic arthritis that was published in Arthritis and Rheumatism in October, 2005. Adept is our pivotal phase three trial in psoriatic arthritis in which patients are given Humira 40 mg every other week, mono therapy, compared to that of placebo. This was for six months. Patient achieved ACR scores comparable to what we've seen with other anti-PNF. ACR20, 50 and 70 of 57, 39 and 23% respectively. However, patients on Humira achieve approximately 50, 75 and 90 scores of 75, 59 and 42% which is only comparable to that of Infliximab, another monoclonal antibody, but superior to what we have seen with other biologic indicators for psoriatic arthritis.

Our Premier study was published in Arthritis and Rheumatism last month and it is our study that showed combination therapy in patients with early aggressive rheumatoid arthritis. Giving Humira with Methotrexate to Methotrexane naive patients produced superior outcomes to Methotrexate or Humira alone in achieving as well as sustaining clinical outcomes and inhibitional structural damage. The combination of Humira plus Methotrexate induced remission in approximately 50% of these patients.

Man: Dr. Ishikawa, I'm going to have to ask you to wrap it up here.

Dr. Ishikawa: Sure. Okay. As far as our safety, currently in our global safety clinical trial data we have over 10,000 patients currently that receive Humira. Of this, this is out to August 31, 2004, 271 patients have been treated with Humira for more than five years and our safety trial of Adalimumab in RA showed no statistically significant difference between Humira and placebo in adverse events.

Man: Thank you.

Dr. Ishikawa: Thank you. Any questions?

Man: Okay. Next is Johanna Lindsay.

Ms. Lindsay: My name is Johanna Lindsay and I'm the director of Programs and Services for the Arthritis Foundation, with the Pacific Northwest Chapter. We just incorporated Oregon into our territory.

I'm here on behalf of 1.2 million people in our state that have arthritis and about a half a million of those actually have functional disabilities from their arthritis. Many of those have these forms of arthritis and have them at a much younger age. In Washington about 10% of adults ages 18-44 have arthritis. And 45-64 year olds have more than 1 in 3 people with arthritis. Among Americans nationwide we have about 5% that have disability from their arthritis. We don't have any numbers for Washington State in particular, but we do know that it's a pretty high level of disability.

As you probably know, arthritis does encompass a wide range of arthritises and about half of those are these auto immune or inflammatory arthritises. We only have just recently had medications that can effectively treat them.

In the six years I've been with the foundation, it's been truly incredible to watch the changes in treatment that we've had because of these new medications. The increasing number of treatments available have given physicians a broader range of options to address difficult to treat disease, both because of variation in patients and types of arthritis. Most importantly it means that patients have second, third, fourth and occasionally even fifth options in addressing their disease when treatment options fail.

I've talked with many patients in my six years here for whom successful treatment has meant the difference between increasing disability and the ability to resume their lives. With respect to our constituents, it's very important there be as many options available as possible. Not only is there great variability among the patients, but also in the response to these medications.

We have two young adults I'd like to tell you about briefly. One's a 20-year-old young adult. She was diagnosed at 13 with juvenile arthritis and was lucky enough to be treated at about 14 with one of the biologic medications and has been on that medication now for about five years. She is now looking forward to paying her first electric bill. Five years ago she was worried about whether or not she was going to be able to live on her own. The options for her in treatment have made a difference between working and receiving state supplements.

We have another young adult, he's in his 30s now. He has ankylosing spondylitis and failed his first biologic that he was on. Now he receives another one and has been able to go back to work and he's actually doing rock climbing with our young adults group.

So the options that they've had in working with their rheumatologists really do make a difference.

From our perspective, if you can give as many choices to the rheumatologists treating these patients as possible, it will make all the difference in the world for our constituents.

I would also like to encourage you to look at the efficacy rather than cost as the major factor in these medications. You know that not every type of arthritis responds the same way to the medications. Patients really do need to have some options. Thanks for your time.

Man: Thank you. Any questions? Okay, thanks. Finally we have two people. Dr. Goffe?

Dr. Goffe: I'm Dr. Bernard Goffe and I'm a board certified dermatologist in Seattle. I do see Medicaid recipients with psoriatic arthritis as well as psoriasis and would like to express my thoughts and thank you for allowing me to do so.

I'm speaking to you as a nationally recognized expert in the field of psoriasis and psoriatic arthritis. I was a co-investigator in the first study of the biologics in psoriatic arthritis and psoriasis using Etanercept which is referred to as #32 in the Oregon Review and bibliography in the Lancet in July, 2000. I have studied all of the drugs you have reviewed and are currently a consult involved in the studies with Abbott, Amgen, Viogen, Centocor and Gentec.

We need the drugs under discussion because the severe side effects…frequent side effects associated with Methotrexate and other standard drugs, their lack of efficacy as well as the fact that only the biologics have been demonstrated to stop joint destruction. There are three currently indicated biologic treatments for psoriatic arthritis and three for psoriasis. I ask that you consider providing access to all of them. You have been provided with copies of the registrational trials which illustrate the efficacy and the safety of Enbrel, Humira and Remicade in psoriatic arthritis and psoriasis. There exists no head to head data that would provide us with comparison efficacy or safety. If it's the intent of Washington Medicaid to select a single preferred therapy, then it's important they recognize the special needs of the Medicaid population, particularly considerations of safety. If you believe that TB is more prevalent in a Medicaid population then you should be aware that there are no FDA black box warnings pertaining to TB in the Enbrel package insert. These warnings do exist, however, for the other drugs.

As a practitioner it is nice to have access…more than nice, it's important to have access to all the therapies. However, if you intend to select only one, Enbrel for reasons of convenience, safety and long term experience has been my personal drug of choice. Let me reiterate, however, that since we often see patients that for unexplained reasons respond to only one of the three drugs you have been talking about, and not to the others, we do need them all. It seems prudent to have at least one therapy with a psoriasis indication on your preferred drug list. We do see patients disabled by psoriasis as well as psoriatic arthritis. I've seen patients resume a productive life because of these drugs without the concerns of cirrhosis of the liver,

[inaudible] as well as potentially fatal drug reactions that are seen with Methotrexate and some of the other systemic drugs. The biologics have virtually no drug interactions and our pregnancy category B rather than category X as the other systemics.

For psoriasis I would like to have Raptiva as well as Amevive available, but again if only one is available my preference would be Etanercept. Thank you for your time. I would be happy to field any questions you might have since there are no dermatologists on your commission.

Man: Thank you. Are there any questions? Thank you. According to my list, I don't have anybody else signed up but I want to check and make sure that's the case, to talk about the immune modulators. Okay. Dr. Gartlehner, are you still there?

Gerald Gartlehner, MD: I'm still here.

Man: I hope perhaps you were able to hear the comments of the stakeholders. I was going to open it up and see … to committee members to see if they had any other questions based on the input. Are there further questions for Dr Gartlehner from committee members?

Okay, well, Dr.Gartlehner, thank you very much for your time. We appreciate it. It looks like there are no other questions. So we can let you go.

Gerald Gartlehner, MD: Okay. Thank you.

Man: Take care.

Gerald Gartlehner, MD: Bye.

Man: I think we were originally scheduled to have discussion after lunch but we're actually, amazingly enough, ahead of time. It's a luxury we don't often have. Why don't we…I think we can go ahead, if it's okay with everybody and just jump right into to discussion. Just wanted to elicit any general comments regarding this class of drugs. Bob?

Robert Bray, MD: This is Bob Bray. I think that this class is very similar in this instance to the prior class where I don't think the evidence allows us to choose between drugs given the variety of indications and the lack of data. I would suggest that we consider doing the same and not identify any drugs in this class as being part of the preferred drug list because of those reasons.

Vyn Reese, MD: Dr. Reese. I don't agree. I think that these drugs have really changed the practice of rheumatology amazingly for rheumatoid arthritis sufferers and I think that we need to have a drug in the PDL for one of the immune modulators needs to be on the PDL. I think that they also have different indications too. After reading the extended review and the slide presentation, it's clear to me that there's nothing for Crohn's disease but Infliximab. And if we're going to have a drug for Crohn's disease then Infliximab would be the drug. That's for the severe Crohn's which there is nothing else that will

actually treat it. So I think that we probably need to add Infliximab for that indication. I think Etanercept is safer, been out liner, I think it should be on the PDL for the other indications. I think we should have those two drugs. Humira hasn't been out as long, it doesn't have as long a track record. It may be more efficacious and have less side effects than the others. I don't think there's as much data on it so I would maybe not have that drug on. But I think the other two should be on for those indications that they are approved for. They are very expensive, there is no question about it. They are really big budget items so it's quite…but I think one of them has to be on. They have really changed the management of rheumatologic disease and they've got to be…you have to have one of these drugs on. I think Crohn's disease, severe Crohn's, Infliximab is what the GI docs use. We have to have those drugs even though they are very expensive. I don't like that they're so expensive, but I think we are forced to have them on the PDL.

Robert Bray, MD: Bob Bray again. I agree with you that they should be available. But I think that availability can be done through prior authorization and having some more control over the use of the medications and where they are appropriate than placing them on the preferred drug list. I agree with you about their importance and I agree with you that they should be available. I'm concerned that they may be way too available on a preferred drug list and having them available through prior authorization is something that may work better.

Vyn Reese, MD: I think when we have one preferred drug, though, it gives a chance to actually have a stake and bargain with that company for that drug. That may give a pricing advantage there and I think it's …I don't think everybody's going to be using these drugs. I think they are not widely used in practice except by rheumatologists and GI docs. That's been my experience. I don't know if it's the same elsewhere. That's my experience with the drugs, but maybe you know more about that.

Robert Bray, MD: Just of interest I received this week a mailing from a company for one of these drugs for the indication of psoriasis. I don't have an argument that it may be helpful in severe cases of psoriasis, but I'd point out that they appear to be targeting generalist physicians for the use of these drugs. I think that my concern is if it is very easy to use these drugs, that I think we may see over utilization of the drugs and that's where I'm concerned is that maybe having those procedures in place to allow the appropriate use, but to also help avoid possibly some over utilization which could be potentially dangerous. I think that might be a better way to go.

Man: Hi, this is [inaudible] current right now what is the process for obtaining these medications?

Woman: Right now we do have all the drugs on a form of prior authorization and expedited prior authorization. Basically the criteria is based on their indication, based on the specific dosing guidelines. We try to put everything in that EPA criteria to guide the appropriate use of the different drugs.

Man: I'd add also just in parallel for Uniform Medical where things stand there too.

Woman: For Uniform Medical plan, these drugs are in our specialty drug program so they are all in our tier three but they are limited to a 30 day supply and they must come from our specialty pharmacy.

Man: Are there comments? Janet?

Janet Kelly, Pharm D: Jack, I had a question about that specialty pharmacy aspect. I understand that for the medications that are self administered. What about the medications that are like the Infliximab where it's given as an infusion?

Woman: We don't require them to get it through the specialty pharmacy if the doctor provides the medication. If the doctor is giving the patient a prescription and having them get the medication and take it to the doctor's office for administration, then they are required to go through a specialty pharmacy but we are not requiring the doctors to order it from there to administer it in their office.

Man: And does being listed on the PDL in any way potentially influence the tiering?

Woman: That was one of my questions, was trying to figure out how that would impact us. I don't think that we would be able to change their tier status depending on which one was named as preferred because of the benefit structure we have put them all in tier one.

Man: Tier one or tier three?

Woman: They are tier one.

Man: Tier one.

Woman: So they have the lowest co-pay. They are a $10 co-pay per month.

Man: Are there other comments or…? I guess the…Jeff, did you have something?

Jeff Graham, MD: [inaudible]

Robert Bray, MD: You know, Bob just commenting…I think on your observations, I think that it appears that currently the medicines are available with expedited prior authorization. And the…I guess the question that I would have is…I'm a generalist physician as well, so I don't prescribe these and I don't really intend to. Bu for somebody who's a gastroenterologist or rheumatologist who are prescribing this on a regular basis, is sort of part and parcel of their practice, whether …just from an administrative standpoint and so forth, whether it's …the issues of utilization should be addressed through keeping a medicine available through prior authorization as opposed to using other mechanisms that we use, and this is actually specific to Medicaid with DUEC with drug utilization reviews and so on and so forth. And it does seem that there are other medications that we have chosen to put on the PDL that while not quite as expensive would sometimes…I think always it's the case that whoever is writing for a medication it's their responsibility to be sure that they know how to use the medicine appropriately and safely. I just would raise that as a…I think it's a differential point

around how do you manage utilization? Do you do it at the point of the PDL or do you do it through other mechanisms?

Jeff Graham, MD: This is Jeff Graham. I did want to point out that some of the drugs that we do have as preferred drugs still have EPA on them. I would suspect that HRSA would probably continue to do that with these drugs, I'm not 100% sure of that, maybe Siri has a better thought about that.

Woman: As you were talking I was trying to visualize what we would do. Given what I think is your section, Dr. Reese, is that if we had Enbrel as a preferred drug and Remicade would be for special population and then the rest of them would require prior authorization.

Man: I don't know whether…I would be worried that the generalists would prescribe them, but not very. That could happen with marketing goes that way. That would be a real worry. I agree with Bob Bray that that would be a concern, that if people were prescribing it for mild psoriasis, that would not be a wise move for the state or anybody else. I don't know whether some sort of prior authorization would still need to be done, but whether we had a preferred drug with prior authorization, that's another issue.

Woman: As a matter of fact, the very last drug class that we looked at when we looked at the anti platelet, we chose two drugs as preferred drugs that will still stay on EPA. So we are in the process of working with that drug class and implementing it April 1st with those drugs requiring PA for this specific indication. And then [inaudible] was just not preferred.

Woman: One thing I wanted to say listening to discussing this is it seems like sometimes you are jumping right now you are going to control the utilization of the drugs. What I wanted to bring it back to is that if you listen to the evidence and something is more efficacious and it's better, then this is also an educational practice for us and for any practitioner that's out there. I think that as you worry about utilization, you can find different ways to do that, but we also want to steer people towards the drugs that work the best and are the most efficacious. I think it's even worse if you put all the drugs out there and people are using them and they're not working. That is not any good either. As I hear it, if there's more evidence for something to be on the preferred drug list, that's what you would want, and you wouldn't want the utilization of the drugs that don't work as well.

Man: I think what we've heard is we really don't have any data with respect to relative efficacy and safety. So we really are unable to make any comparisons. I think what we do know is that there is one medicine that is effective in one condition and that is Infliximab. I think one way of doing this would be if we were to make a recommendation with respect to the PDL, would be to say that the PDL must include Infliximab and then I would suggest one other agent or agents that are effective that we found these other agents to be effective in the treatment of these other rheumatologic conditions that a second agent probably should be available if only because Infliximab is only by I.V. infusion. So constructing something along those

lines if we were to go the PDL route and it sounds like for all intents and purposes there's going to be expedited prior authorization with respect to Medicaid either way.

Man: I think there is greater efficacy for Adalimumab, Etanercept and Infliximab than Anakinra.

Man: I agree with that.

Man: They ware equally efficacious.

Man: We would have to call out those. I should have specified that.

Patti Varley, ARNP: This is Patti Varley. That's what I was feeling I was hearing from the data, myself, is exactly that.

Man: Are there any other comments at this point? Anybody? I'm wondering if anybody would be willing to make a motion one way or another? Bob, I think you have a point of view and I think there is an alternative point of view that's been discussed here. It seems to me that we could start some place, one place or the other, with a motion.

Man: I'll go ahead. I think the motion will have to be made for various indications since some of the drugs aren't approved for all of them, so that would be my…I think probably make two different motions because there are different drugs. My motion…hold on…

Man: That's it. Donna, did you want to…

Donna Marshall, Pharm D: [inaudible]

Man: As long as you can type and then we can project later, that's fine.

Man: First I'm going to talk about indications for rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritic and ankylosing spondylitis. We didn't really talk about plaque psoriasis in the review so I'm going to leave that out. But those are the indications that I'm going to be discussing, and then a separate one on Crohn's disease, which is a different drug.

After considering the evidence of safety, efficacy and special populations for the treatment of rheumatoid arthritic, juvenile rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, I move that Etanercept or Enbrel is safe and efficacious. No single medication in this class …I'm not sure what that line is with the blank… No single targeted immune modulator, okay we'll insert that there, is associated with fewer side effects than special…that's not really what I wanted to say…I think I wanted to delete that line, or say no other targeted immune modulator is associated with fewer adverse events in special populations. Etanercept cannot be subject to therapeutic interchange in the Washington preferred drug list. I would make a separate motion…we need to include in this one first that there needs to be a separate motion regarding Crohn's disease. Why don't we talk about this…

Man: …it totally needs to be on… the Infliximab for Crohn's so we can work…we are just going to look at this motion here for a moment and just …before we do anything else just ask if there's any comment or any why in which people would react to that as a motion.

Man: The concern that I would have I guess is although that is true, there are for some of those indications other drugs that were studied and are not clearly…you can't clearly identify differences between them and Etanercept. I would just point that out. I guess it makes it sticky but if you were going to do it this way, it seems like we might need to look at each individual indication because there are differences in the evidence by indication.

Patti Varley, ARNP: This is Patti Varley. I also have a problem with the way it is listed there too when there is…as you go through it, evidence that at least three of them have some indication to being more useful than the others and yet we are only listing one.

Man: So one possibility then would be to have a motion relative to each indication and in one case, that being Crohn's disease, there would only be a single agent, and with respect to other conditions, it would depend. There would be multiple agents.

Man: We could do it by each indication and we also, Humira has also been approved for RA and psoriatic arthritis and it's very efficacious, less is known about it. We could add Humira into that and we could do it by every separate indication if we wanted to.

Alvin Goo, Pharm D: Hi, it's Alvin. I'm wondering if we first decide we want to put this on the PDL, this class on the PDL first before we move on. I don't know about having to go through each indication and choosing a first line agent.

Man: That sounds like a reasonable approach because maybe we should address that before we get into this in detail. Don't erase this, Donna, but what I'd like to do is look at Alvin or Bob and see if he would want to put forward a motion and we can have some discussion and then vote on that relative to…it sounded like your thinking was to table this at this time. Or not, I mean…

Patti Varley, ARNP: This is Patti Varley. I will attempt in a very naïve way to just say when I was listening to the data presented as I made what I call my little cheat sheet, I had two drugs on the list of six that had no data. That left me four. I had data that showed…three had better efficacy than one. In my mind the three that were left needed to be on the left because there was the evidence in front of me saying that.

Man: I really agree with you too. The only reason I had put Etanercept up there is that it's easier because it's got more indications. But that's the honest evidence based way to make the motion.

Man: I like that. Being honest and being evidence based.

Janet Kelly, Pharm D: This is Janet Kelly. I agree with that. We have those three drugs and I think when we say there is evidence that they are safe and effective and then the rest of where it's going to be, can be done with the EPA for the Crohn's disease, obviously

the Infliximab there. But we don't really have a whole body of evidence that says were everything needs to go. We do know that those two drugs are safe and effective so we can say that. And leave the rest of it to the agencies to do.

Man: And do that by indication.

Man: And we would say they were only approved for rheumatoid arthritis and psoriatic arthritis because that's what the common indications are.

Man: So what I'm hearing is they are sort of, again, we're working through some of the details of what Vyn had started here and yet I think there's also some opinion that perhaps we should table this and I think Alvin's right. I think what we might want to do if someone is willing to put for the motion. If not, we can go on with the discussion that we're having. But if somebody would like to put forth the motion and you can soft of address whether or not we want to table it at this time and if we table it, then we can…we're pretty much done. If not, we can continue with this other discussion.

Robert Bray, MD: This is Bob Bray. I would move that we table the discussion of this class of drugs for the purposes of PDL.

Man: Actually, we…

Man: Second.

Jason Iltz, Pharm D: This is Jason. Second.

Man: Okay, so there is a motion to table this discussion of the immune modulators. It's been seconded. Is there any further discussion at this point? Okay, then I think what we'll do is vote on this and actually I think we need to probably vote individually because I think there is some difference of opinion which is okay. So, if you want to start with Patti, no.

Man: Are we voting to table? Yes.

Jason Iltz, Pharm D: This is Jason. Yes.

Robert Bray, MD: Bob Bray, yes.

Man: Did somebody…yes? Five to four? So the motion does not…I voted no. Okay, let's do it one more time. Five, four not to table. The motion does not pass. So we can continue with the discussion of how to move forward and present the motion. Jeff, should we…would this be a good time to break and then can we come back after lunch and finish? What's the…Okay. We've got the time. What we're going to do at this point is adjourn right here until 1:00 and then when we reconvene we will finish out with this class of meds. Thanks.

Man: I think we are trying to get a hold of people at OHSU because we will be able to start the antiemetics somewhat earlier. So if folks could take a seat. Angelo? So we are

going to take up here with the immune modulators and I think we're looking at trying to develop a specific recommendation or recommendations with respect to the medicines we heard about this morning. And I know Vyn's been working on maybe trapping something over here. Do you have anything? One way of going here is just to take it by individual indications in terms of what we know about which would be rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn's disease and juvenile rheumatoid arthritis and just come up with…

Man: [inaudible]

Man: I think there's two ways of doing it. One is to go individually through every disease and talk about what's indicated. And the other way is basically to say after considering the evidence of safety, efficacy and special populations for the treatment of the rheumatological diseases of which they have FDA indications, that way we would cover the ones that they are indicated actually to treat. I think that evidence wise we needed to include Humira, Enbrel and Remicade, all three basically. It should be Etanercept, Adalimumab and Infliximab. Except I would say the use of targeted immune modulators to treat the rheumatological conditions for which they have FDA indications… for the treatment of the rheumatological conditions for which they have FDA indications. That's not Alefacept, it's Adalimumab which is Humira. It's A-D-A-L-I-M-U-M-A-B. It's not immunologic conditions. It's rheumatologic conditions on the top. There you go. There are immunologic conditions too. And then after Infliximab it should be are safe and efficacious. And then I would delete Etanercept down in the last sentence and just…these medications can not be subject to therapeutic interchange. We need a separate one…we need a separate motion…we should act on this motion first and there is a separate motion for ulcerative colitis or Crohn's disease. Yeah. Inflammatory bowel disease.

Patti Varley, ARNP: Patti Varley. Just out of curiosity, can you add that to your statement?

Man: These are rheumatologic disorders and the others are GI, basically. So it's like…if you really [inaudible] I guess you could, but it's certainly going to be a very messy motion. It might be a bit clearer and crisper because it's a different sort of type of condition, I think is what you're saying.

Donna Marshall, Pharm D: This is Donna Marshall. If you don't specify rheumatologic conditions and just say for their FDA labeled indications, do we cover that? Because you have Infliximab listed there.

Man: You could just…You could actually go back to what you had before. For the treatment of immunologic diseases for which they have FDA indications.

Jason Iltz, Pharm D: This is Jason. Just to point out, just so we're all inclusive here, this review's a little different because it actually did include effectiveness stated as well. I know very limited, so maybe we should add after considering the evidence of safety, efficacy, effectiveness and special populations. They did at least look at that. I know there wasn't much data. I don't think you will change your statement saying safe and efficacious. Just to point that out.

Man: You want to add after considering the evidence of safety, efficacy, common effectiveness…I'm speaking for Carol I guess since she can't be here. She always wanted to get effectiveness in there.

Woman: Do you want to put effective, safe, efficacious and effective as well?

Man: I think just safe and efficacious. There are efficacy studies and effectiveness studies. But that's not talking about the studies. I think I would leave that the same. That's how we crafted the other one.

Man: And I suppose because Infliximab is the only one that has an indication for Crohn's disease we don't have to call that out specifically. Would that be correct from…? So as people look at that, are there any other thoughts or concerns that people want to raise at this point? Suggestions?

Robert Bray, MD: I have a question. This is Bob Bray. Maybe this is a question for Siri and others as far as trying to avoid unintended consequences. The way that reads, would that then state that all three have to be on the PDL?

Man: No.

Robert Bray, MD: Would that allow for only one to be chosen on the PDL? But no more than that?

Man: As I understand it, it's just one…you could pick one of those drugs for each indication. Or however you wanted to do it, basically.

Man: My only concern there then is that you could go only with Infliximab which theoretically which can only be administered by I.V. and whether or not we want to specify that there has to be one that is administered in some other way.

Woman: You could indicate that we are required to have more than one drug as preferred if you so choose.

Patti Varley, ARNP: This is Patti Varley. That being said, if that's the case, then you would want to make sure you cover any special populous for which only one of the three covers.

Woman: [inaudible]

Man: Except for Crohn's disease there is not a self administered one that's approved, right? So, right.

Man: [inaudible]

Man: My comment is, and I'm just trying to make sure we don't do something we didn't intend, if we didn't say anything more about Infliximab, then we haven't covered that indication because we haven't said anything here that says, yet, that says Infliximab would have to be on the PDL.

Man: At the risk of repeating ourselves, should we just specify that Infliximab must be included and as well that self administered preparation must be included?

Man: So the last sentence, Infliximab must be included for the treatment of inflammatory bowel disease, for Crohn's disease. And a self administered medication must also be on the formulary or PDL…for other indications. None are approved for…

Jason Iltz, Pharm D: This is Jason. I think I personally would still like to see some sort of prior authorization criteria with this too. That's probably going to happen, but without making the statement it may not. So my thought is that if the committee is in favor of saying something about it remaining as a prior authorization medication, I think we should do so.

Man: Jason, I understand where you're coming from and agree sort of that prior authorization might be advisable, but I think my sense is that given our role here, and given that we're talking not just about Medicaid. This is Uniform Medical and L&I as well where different sets of rules and so forth, I think if there is going to be a discussion of prior authorization or controls and it's more properly addressed in the DUEC and not in the context of the motion that we put forward here. Is that…? Okay, so then do you want to just read it one time here?

Man: After considering the evidence of safety, efficacy, effectiveness and special populations for the use of targeted immune modulators for the treatment of immunologic conditions which there are FDA conditions, I move that Etanercept, Adalimumab and Infliximab are safe and efficacious. No other targeted immune modulator medications are issued with fewer adverse events in special populations. Infliximab must be included for treatment of Crohn's disease in addition to a self administered agent for other indications. These medications cannot be subject to therapeutic interchange in the Washington preferred drug list.

Man: That's the motion that's been put forward.

Patti Varley, ARNP: Patti Varley. I'll second.

Man: So it's been seconded. Is there any further discussion? All right. All those in favor please say aye. Opposed same sign. So there is one nay. The motion passes. So I think next we're trying to get folks on the line from Oregon. They actually weren't supposed to join us until 2:15.

Man: [inaudible]

Man: I think that's a good idea. Why don't we just juggle the agenda here. So we're going to now reconvene instantaneously as the DUEC here and I think do we need to approve the minutes from the last…may be we can just give people a second to find those and take a look. Why don't we table approving those until the next time. I think we can…we'll do that next time around. So we'll to the two. We can move right into today's presentation. So it said that Jeff Thompson was going to be here but I don't see Jeff.

Man: I can introduce the subject of…we are bringing forward some recommendations for the use of drugs in the treatment of ADHD. These come from our mental health workgroup which consists of a large group of folks from the mental health community plus state folks plus representatives from the industry and also other stakeholder's advocacy groups. June Bredin is here today to do that. June, I think I'll just have her…she has a long list of things that she does and I think that would be very helpful for us to know exactly how she is involved in that work group and also maybe tell you a little bit about the work group.

June Bredin, MD: I'm June Bredin. I'm a family physician who since 1999 has worked full time for ADSA DDD both at Rainier school and for five years I was the medical director at Frances Head and Morganson. Additionally I wear another hat. A workgroup that I'm also the chairman of the mental health and substance abuse committee for the Washington Academy of Family Physicians. I also represent the WAFP on the work group. It really is a broad cross section both of medical and advocacy people. We have quite lively debate about issues. What this presentation is, is actually a fairly brief presentation, three parts. Number one, what criteria and thoughts went into making recommendations regarding appropriate ADHD drugs for inclusion, then gathering information especially from child psychiatry groups including the people at Children's especially. And then we have some general recommendations coming from that. I'd like to remind you that in this particular diagnosis both for children and adults, probably a vast majority of our clients are served by primary care physicians, both pediatricians and family physicians in the pediatric group and family p physicians and primary care internists in adults. We try to be very thoughtful in making recommendations that were both appropriate but not too restrictive both for primary care and psychiatry providers in this diagnosis.

With that we will go to the next slide. When we first met and kind of started out our framework, we did look at the Oregon evidence based practice centers, information on what evidence was available in these drugs both in children and adults. And then Dr. Childs presented fee for service Medicaid data regarding what the prescribing patterns within out state both for maximum doses as well as combination. Sometimes combination of multiple medications for this diagnosis. As we looked at that, we really, as we began to make our recommendations, we really tried to make it a primary concern, safety as well as trying to make guidelines that could encourage people to most expeditiously get to good treatment safely. Because we saw…there was a clear minority of patients who were on very high doses of stimulant medication as well as combinations with anti psychotics and sedatives. We wanted to set some guidelines that tried to induce some more uniform practice. So beginning in December and through earlier this month, the work group met on those criteria safety issues as well as pharmacologic basis and the American Academy of Pediatrics guidelines for treatment of ADHD to make that decision. Next slide please.

In this process we included Brian King and several other people from Children's Hospital as well as community child psychiatrists and looked at the quality of research for specific medications and treatment ranges as well as risk of harm especially for over FDA limit prescribing as well as for combination therapy, cost of treatment versus non pharmacologic treatments for ADHD, as you know behavioral modification and educational supports and parental education, also play a very big role

in treating this disease. And were there any vulnerable populations that required a higher level of evidence before treatment such as very young children or people with comorbid diagnosis of, especially in my realm, those with development disability. Next slide please.

After a lot of discussion, we came to the point that understanding that though there is not good evidence in all population groups, we had to balance that with the fact that in those diagnoses where there aren't good studies, there could be some harm from these medications. They are not entirely without side effects especially at higher doses. We talked about historical examples such as use through the 1950s and 1960s of high dose oxygen in inmates and respiratory as well as ophthalmologic complications of that. The fact that such a false positive rate as well as our more recent issues with the top two drugs and safety post marketing experience. Can I have the next slide, please?

So on all of that basis and with a lot of discussion between primary care, advocacy and psychiatry, we looked at what appropriate limits we should have for different age groups as well as higher limits as far as doses. We looked at pharmacological and FDA recommendations and then also looked at our data of what percentage of our population was above both 100 and I think it was 120 and 150% of maximal recommended ranges. We do have a considerable number even of young children who are being treated at very high doses. And also looked at what were appropriate combinations of drugs, specifically whether methylphenidate group drugs, dextroamphetamine group drugs and Strattera should be combined or not and there is not a lot of good evidence that would say that any of those drugs should be combined. We also looked the use of sedatives on a chronic basis in the pediatric population specifically correlating if they were on high dose stimulants and then requiring sedatives as a red flag that there may need to be other diagnosis and evaluation going on for appropriate treatment. And then for non [inaudible] providers, and, again, we have tried to set our recommendation base not on cost but on how to create a structure that would encourage people to most rapidly and faithfully get to good treatment regimens and given that in this particular medication combination, medication group, unlike most other psychiatric drugs, there are two groups of drugs that are essentially chemically identical but have multiple delivery systems and slow versus fast relief specifically of several dextroamphetamine drugs as well as the several methylphenidate drugs. A lot of good data says that there is no increased efficacy to combining across the classes as well as the Strattera but that we need to have the availability of short and long acting agents in both of the stimulant groups and that we should be sending criteria that would say along with the American Academy of Pediatric recommendations that if you fail a methylphenidate drug for lack of treatment response, that the best thing to do is not to stay within that group but move to one of the other groups, either Strattera or dextroamphetamine because you have the highest likelihood of obtaining a clinical response. So trying the set our parameters on that, trying to get people to good treatment quickest. So for that we came up with the tried and failed two preferred drugs because there were at least two of three classes of drugs that could be chosen with the caveat that if there was intolerance to preferred drugs and specifically in adolescents and adults if there was any risk for either cardiovascular risk with stimulants or if there was any concern regarding diversion or abuse. Can I have the next slide, please?

So based on that we did set some maximum dosing guidelines. I think it was amazing that within all the clinicians, everybody very quickly agreed that these were very clear and appropriate guidelines. For the methylphenidate group for those greater than five years of age you can see there that we would have…we would not recommend going above a maximum dose of 120 mg per day. For younger children, greater than 30 mg per day and that we would not approve without review any treatment for children less than three years of age. We have some client members of people who actually already are prescribed greater than those maximum and similarly the 60 mg for greater than five years of age for amphetamine class and 15 mg for those three to five. Can I have the next slide, please?

And this shows a picture of all our pediatric population for a fiscal year 2005 of what the current prescribing practices are. And the circles as you can see, though they don't have lines, have significant overlap that we do have a fair number of children and adolescents that are on both classes of stimulants as well as minorities that are also on chronically prescribed sedatives. This is kind of an issue that we're trying to address as we make up our recommendation for the preferred drug list. Can I have the next slide, please?

So that's kind of the basis of where we got. Any questions?

Man: Thanks. Really very nice. Nice piece of work by the group. Are there comments. Actually, Patti I was wondering if you wanted to specifically comment?

Patti Varley, ARNP: I just have to say…Patti Varley…that I appreciate…I think that the group did a lot of investigating and a lot of consulting to try to maximize the potential of doing it the best they could and getting as much information. As for that I'm grateful because I know even towards the end there were a lot of differences of opinions or I would say at times lack of understanding. I was at least privy to part of that ending of how it went and I feel much more positive of how it turned out.

Man: Are there other comments or questions? Will this then become the guidelines that you follow at Medicaid?

June Bredin, MD: What we plan to do with your approval is that when we implement the ADHD drugs on April 1st, that we would implement age and dose limits as well. And what we've done is we've actually…we are designing the computer edits to stop any order for a child that is five and younger so that we have the opportunity to ask for medical justification for that group of kids. And then we would also implement hard edit for any dose that exceeds either 120 for methylphenidate or 60 mg for amphetamines for an age that is over five. And then somewhere down the line and maybe as soon as May or maybe as soon as June, it just depends on how well all of this implementation goes, we would like to implement the combination drugs. We would like to say it's really fine as long as you're using a short and a long within the same group, like a methylphenidate. But if you are using it across methylphenidate and an amphetamine we'd like to stop those and ask for medical justification. But that would be a separate one, initiative that we would do at a later time. And then the other initiative that Dr. Green talked about is the sleepers. It's a combination of ADHD drugs and sleepers. We would at some point in a separate initiative we would stop those orders to ask for

medical justification. Our committee recommended that for anyone under the age of 18 that if we did approve a sleeper it would only be a one time approval and it would be a maximum of five doses, period. There was lots of talk about these outliers should be very rare and they should ultimately involve a consultation with an expert from Children's, Mary Bridge and such. So they will be helping us make a decision as to whether to deny it or approve those.

Patti Varley, ARNP: This is Patti Varley again. Just for a point of clarification on two things. One is that when you look at your chart and understanding that it would be infrequent, but there certainly are kids who metabolize in a way that they are outside of that, I'm assuming once you ask the right questions and get the correct answers the access would not be denied for them to continue outside those.

June Bredin, MD: That's exactly what we talked about when we had the whole discussion of what is a rapid metabolism. When we talked about people especially that were greater than 150% of the FDA recommendation that those charts at least probably be reviewed or reviewed by what Jeff was recommending was the people at Children's, Mary Bridge [inaudible] one of the Children's hospitals that we have enlisted. But it should be a positive thing. Number one, are we at the right diagnosis because sometimes when kids get to that high a dose they are still not doing well. If the child is doing well and we really think they are a rapid metabolizer then it should be approved. But it's enough to make you think are you going down the wrong path.

Patti Varley, ARNP: Patti Varley again with a second question. You talked about the issue of the methylphenidate versus the amphetamine, is there allowance for the fact that there are at least, again in the outlying population, kids who develop tolerance for one agent versus another who may be switching back and forth between them so they are not taking them at the same time but it may look that way because one week they are filling this one and the next week they are filling for another one.

June Bredin, MD: In fact, we have talked about time limits that we thought in this drug class that probably a 30-day overlap because they are not drugs that you have to take a long time to taper.

Patti Varley, ARNP: Great.

Jeff Graham, MD: This is Jeff Graham. A comment on slide eight, June and Siri, I didn't catch this before, it says for non endorsing providers in the second bullet it says some documentation of intolerance to starting with a non preferred drug. Do you mean intolerance to a preferred drug?

June Bredin, MD: Correct.

Jeff Graham, MD: Okay.

Man: Thanks. I wondered about that. It sounds like the group has gone through…reviewed a lot of material, certainly had a lot of discussion. I'm, wondering if to the extent that providers who want to be more educated can avail themselves of what's the good work that's been done. I wonder if there's any intent to put out something along the

lines of a white paper or post some of the key references that were reviewed and other educational efforts?

June Bredin, MD: Well, you know, before we would implement any type of a new drug initiative, we do the prescriber education at least one month if not two months prior and we have planned to target those prescribers that we have identified are writing for children under the age of five or they are writing amphetamines or methylphenidate over the limit and they will receive a packet of information including the drug history on their patients and, you know, ask specifically a month or two months ahead, could you provide the medical documentation or could you reconsider this so that it could actually be taken care of before there is hard edit that hits on those patients.

Man: And anything more broadly as well? Even amongst those people who might appear like they are doing it correctly in some sense, just making available…

June Bredin, MD: I guess what I would say is that all of this material that we have developed is on our web site. Every opportunity that we have we'll share, telling folks, steering them to that web site.

Man: Any other questions? Angelo do you have any?

Angelo Ballasiotes, Pharm D: Is there going to be any…with regards to consideration to adults or go any further with that?

June Bredin, MD: We did also talk about adults and talked about actually using the same dosing guidelines that we are using for adolescents and realizing that there may be more reasons not to use the amphetamines in adults either for cardiac reasons or for diversion or abuse potential. That would be a reason to get to a non preferred drug using then Strattera and non preferred drugs.

Woman: If you are interested, I just did the statistics and I can tell you that right now we have 634 clients that are five and younger that are receiving these drugs and we have only like 484 over six that are exceeding the maximum doses. So we think that our prior authorization lines can handle that impact.

Woman: Siri, do you know provider wise, are most of them being prescribed by the same provider?

Woman: [inaudible] what their specialty is.

Man: It seems like it might be helpful if we had a formal motion approving these guidelines. I'm wondering, Patti if you would…your having been involved, I'm wondering if you wanted to…

Patti Varley, ARNP: This is Patti. Since there is no template on this I'm just approving the recommendation of the … so that we're recommending approval of the Washington State Mental Health Stakeholders work group ADHD drug therapy safety edit.

Man: Okay. Is there a second? Okay, there's a second. Any further discussion? All those in favor say aye. Those opposed same sign. It passes. Dr. Bredin thank you very much for taking the time to come present this and also I think if there is some way just on behalf of the PNT committee of expressing our thanks to the group that I'm sure got together on their own time to review and put together these recommendations, please do. I think now we're going to switch hats again, am I correct?

Man: I suggest we take a short break while we get things connected.

Man: Would 2:00 be okay, Jeff? Okay. So we're going to adjourn until 2:00 and then we'll reconvene to take up the last topic.

Jeff, are you…So, we're going to get started. Kim Peterson from OHSU is going to join us we hope here in just a minute. There's some background that probably we can just go through collectively to … in terms of the beginning of the presentation and then our hope is that Kim will join us when we get into more details about studies and such. We're going to be looking at anti emetics and why don't we have the first slide here. So again this reviews the OHSU search strategy in terms of…which we have seen before. I guess in this case, in addition to just the usual databases, library databases that were searched, there were also information that …dossiers and such that were submitted by pharmaceutical companies for … I'm not going to be able to pronounce any of these, for the medicines that are listed as well FDA reviews that are available.

Next. Again, this is sort of the usual methodology that is used by OHSU to look at the quality of studies and rate them based on predefined criteria and then only include in the data abstraction…study data abstraction, those studies that meet a certain level of quality and where possible to combine data into a meta analysis although I seem to recall that in this case they were unable to…there was too much heterogeneity and there are no meta analyses with this particular review. Overall grade allocated to the body of evidence for each question.

Next. So in terms of inclusion criteria for this class of drugs, adults and/or children at risk for or with nausea and/or vomiting including retching related to the following conditions, postoperatively either established meaning that a patient is actually experiencing symptoms post-op [inaudible] or preventably. Also in the setting of chemotherapy, radiation therapy and pregnancy.

Next. Here is a list of the interventions or medications in this class that were looked at, is there somebody better? I can never…Emend, Anzemet, Kytril, Zofran and Aloxi.

Next. Inclusion criteria, efficacy outcomes, preventing or reduction of medic events, nausea, vomiting and/or retching and the actual outcome measures that were looked at included proportion of patients that were symptom free, change in mean number of manic episodes, change in symptom severity, number of emesis free days, delay in the onset of medic events, rescue medication use and incidents of serious complications secondary to emesis. As well they looked where it was available at satisfaction, patient satisfaction and quality of life and resource utilization. Safety outcomes include overall adverse event reports, withdrawals due to adverse events, serious

adverse events reported and specific adverse events such as headache, constipation, dizziness and so on.

With respect to study design, for effectiveness or efficacy they were looking at controlled clinical trials and good quality systemic reviews. For adverse events they also were looking at observational studies in addition to controlled clinical trials.

So we're up to results. And we're going to stop here and see if Kim's available to join us.

Man: Two minutes.

Man: Two minutes? So she'll call in? So we have two minutes, so we'll wait two minutes.

Man: It's our fault. We told her 2:15 so we got ahead.

Kim Peterson, MS: Hello, this is Kim.

Daniel Lessler, MD: Kim, can you hear me? This is Dan Lessler.

Kim Peterson, MS: I can.

Daniel Lessler, MD: Great. We just did the background here without you and actually at this point are up to slide nine which is the beginning of the results. I think everybody is pretty much on the same page here. If it works for you just to pick up with the results, that would be great.

Kim Peterson, MS: Sure. Sorry to keep you waiting.

Daniel Lessler, MD: No, that's okay. We are ahead of schedule.

Kim Peterson, MS: I wanted to see if there was anything I wanted to mention that was on the slide that I think might be helpful. Oh, I think it's okay. So I'll start on slide nine.

Daniel Lessler, MD: That's great. And slide nine is up in front of us.

Kim Peterson, MS: Okay, great. So if I just cue for switching the slides, someone will be following?

Daniel Lessler, MD: Yes.

Kim Peterson, MS: Okay, great. Okay, before I get into the results section I do want to note that our message included another important element and that is that we do subject all new reports to an extensive peer and public review process and that this final report has been through these processes and it reflects changes that we made based on the comments we received. And that wasn't in any of the previous slides, but that is part of our process.

So now I'll go onto the results and so this slides provides an overview of the total number of studies included in this review. And as you can see newer anti emetics

have been most widely studied for the prevention of nausea and vomiting associated with chemotherapy. And, fortunately, there were a substantial number of head to head trials in this area. Unfortunately observational studies were few and were not useful for evaluation of series adverse effects due to flaws in their patient selection and outcome ascertain message. So the results from the observational studies will not be discussed in this presentation.

I also wanted to note that no study was classified as an effectiveness study and that was mostly due to the types of outcomes assessed and the use of stringent eligibility criteria the prohibited patients that were suffering from other concurrent illnesses and undergoing other treatments from participating. These patients in these trials were not your average patients.

Next slide, slide 10. Prevention of postoperative nausea and vomiting. So the next six slides summarize the evidence that is related to the prevention of nausea and vomiting associated with surgical procedures and so in summary head to head trials included a comparison of Dolasetron to Ondansetron and Granisetron to Ondansetron but didn't compare Dolasetron and Granisetron to each other and head to head trials focused mainly on clinical symptoms. So we did rely on indirect evidence from active and placebo controlled trials for comparison of Dolasetron and Granisetron and for evaluation of satisfaction and hospital stay outcomes.

Next slide, 11. Prevention of postoperative nausea and vomiting in adults. Focusing on the comparison of Dolasetron versus Ondansetron, said the majority of the evidence related to the prevention of postoperative nausea and vomiting involved adults and the comparison of Dolasetron and Ondansetron was the most widely studied and we were able to include evidence from five head to head trials here. So dosage forms and levels ranged across these trials and there was variability in the types of surgical populations involved. But outcome reporting message were consistent across these trials and all measured the proportions of patients that were classified as responders at 24 hours post surgery. With response generally defined as the absence of one or more emetic events including nausea, vomiting and/or the use of rescue medications. Across these five head to head trials Dolasetron and Ondansetron were generally associated with similar response rates. There were generally no differences between those drugs.

Now, patient satisfaction and hospital stay outcomes were, as I said, only reported in placebo and active control trials and results from these trials suggest that Dolasetron was superior to placebo in improving patient satisfaction and in reducing hospital stay time whereas Ondansetron was not, had similar effects to placebo for both of those outcomes. However, drawing conclusions about the indirect comparative efficacy of Dolasetron and Ondansetron based on these placebo controlled trials may not be appropriate due to heterogeneity in populations and outcome measurement methods across these trials.

And finally, adverse event reporting was surprisingly severely limited in these trials and so of the five trials, we included only one reported adverse effects and in that trial there were no differences in rates of overall or any specific adverse events between Dolasetron and Ondansetron.

Okay, next slide, 12. The comparison of I.V. Granisetron and I.V. Ondansetron. So there were also no consistent differences between I.V. Granisetron 1 or 3 mg and I.V. Ondansetron dosed at 4 mg in rages of 24 hour response across two head to head trials in populations that consisted of mostly women undergoing either radical mastectomy or laparoscopic cholecystectomy. And, again, there were also no differences in adverse effects between Granisetron and Ondansetron, but these were only reported in one of the two trials.

Okay next slide, 13. Indirect comparison of Dolasetron versus Granisetron. So as I mentioned, the head to head trials only discussed the comparison of Dolasetron or Granisetron to Ondansetron but not the comparison of Dolasetron and Granisetron to each other. So for this reason we looked to placebo controlled trials to try to make indirect comparisons between these to anti emetics and both were associated with significantly higher complete response rates than placebo. So in three placebo controlled trials for Dolasetron, Dolasetron was superior to placebo. And then in one trial for Granisetron versus placebo, Granisetron was superior.

Now, as you can see in this slide, that absolute response rates appear greater in the one trial of Granisetron so 61.7%, rates ranged 61.7 to 63.4% and they seemed smaller in this study of Dolasetron numerically smaller. But we didn't make conclusions about the indirect comparative efficacy based on these trials, because, again, there was heterogeneity in populations between the one trial of Granisetron and then the three trials of Dolasetron.

Okay, so next slide, 14. Comparison of Dolasetron and Ondansetron in children. So we are onto the evidence in children. In children, Dolasetron and Ondansetron were associated with similar 24 hour response rates across the only two included head to head trials in children undergoing surgical procedures and, again surprisingly, rates of adverse events were not reported in either trial, so we have no evidence there. And head to head trials did not report satisfaction or hospital stay outcome and in this case there was only limited evidence available from active and placebo controlled trials. And the evidence was, again, insufficient for making indirect comparisons and again mainly due to heterogeneity and population and outcome reporting methods. But in general Ondansetron was more widely studied and was superior to placebo in improving patient satisfaction and hospital stay outcomes in three trials whereas there were no differences between Dolasetron and placebo in one trial.

Next slide, 15. Comparison of Dolasetron and Granisetron in children. So we did evaluate placebo controlled trials to address other gaps in the head to head evidence for children. We screened numerous placebo controlled trials for similarities and population design and outcome reporting and there were only two that met criteria for possible indirect comparisons and these two trials happened to evaluate Dolasetron and Granisetron respectively versus placebo and results from these trials suggest that Granisetron was superior to placebo in reducing hospital stay time where as there were no differences between Dolasetron and placebo. Again, we do have uncertainly about what to make of these results. In this case the uncertainty is due to the…we are uncertain about the comparability of dosage levels used across these studies. So Dolasetron was dosed according to the product label, whereas there were no product

label guidelines for Dolasetron so we don't know which, if any, of the Granisetron doses 20, 40 or 50 micrograms/kg as used in this study is optimal and the most comparable to the Dolasetron dosage that was doses per product label which was .35 mg/kg. Again we have some what looks like disparities in evidence but really can't draw conclusions about it at this time.

Okay, slide 16, now we're onto the treatment of postoperative nausea and vomiting and as you can see the evidence is much less robust in this area and we had to rely solely on indirect comparisons from placebo controlled trials that only involved evidence for Dolasetron, Granisetron and Ondansetron but fortunately a quantitative analysis from a previously conducted good quality systematic review was available to provide the basis of our conclusions about the indirect comparative efficacy of these drugs and then we also analyzed seven additional trials that were published subsequent to the systematic review.

Slide 17. So the Kazemi-Kjellberg et al was the good quality systematic review that included 11 trials and in their quantitative analysis which though only focused on efficacy and focused on prevention of further nausea or vomiting within six to 24 hours and so we were unable, or they were unable to make indirect comparisons related to the outcomes of prevention of further nausea because data was only available for Granisetron for that outcome. So we were looking at only the indirect comparative efficacy for the outcome prevention of further vomiting. The table on this slide reflects the ranges of numbers needed to treat to prevent one additional case of further vomiting for Dolasetron, Granisetron and Ondansetron at six and 24 hours. As you can see the numbers needed to treat are fairly similar across the drugs and so really don't suggest that any one of them is superior than any other in preventing further vomiting.

Okay, next slide, 18. And as I mentioned, we did search for and included, and analyzed an additional seven trials that were published subsequent to that previous systematic review but these did not add evidence of any drugs or outcomes that were not already included in the Kazemi-Kjellberg analysis and the results in those studies of the last Dolasetron, Granisetron, Ondansetron were similar and consistent with the findings in the Kazemi-Kjellberg review.

Okay, next slide, 19. Okay so the next eight or so slides pertain to the prevention of nausea and vomiting that's associated with chemotherapy. This is the largest body of evidence in this review. And there were numerous head to head trials that met the inclusion criteria and as you can see most of the research focused on the comparison of Granisetron to Ondansetron. There were numerous studies, 31 total head to head trials, and the number in brackets pertains to the number that we rated poor quality. So there was actually a high proportion, well, relatively high, that were rated poor. So we really only included 20 in our evaluation, but that's actually a pretty substantial amount. So we were happy about that. And we also reviewed active and placebo controlled trials to address gaps in the head to head evidence, but they didn't provide opportunity for indirect comparison due to heterogeneity but they did provide the only evidence that supports the efficacy and safety of Aprepitant and provide the only evidence of quality of life outcomes but only for Ondansetron.

Okay, next slide, 20. So this slide focuses on the comparison of Granisetron versus Ondansetron, the largest body of evidence in this area and this slide focuses on the findings in adults. And there is a type-o on the slide. As I mentioned the number of head to head trials is 20, not 18 as stated here. Sorry about that. Okay, these trials involved more men than women that were generally aged 47-64 years and were undergoing chemotherapy of various levels of emetogenicity for various malignancies. The trials were heterogeneous. But regardless of the differences, and other differences such as in dosage levels and form, there still were very few differences across all of 10 of the 20 trials that focused on the outcome of rates of patients with no nausea and no emesis or the combined outcome of no nausea and no use of rescue medication within 24 hours or beyond. And then there were also no differences in the … no consistent differences in the other 10 head to head trials that reported outcomes that separated out the nausea and vomiting response rates. So those outcomes were either no nausea or a separate outcome, no vomiting. So that the other…the combined outcome is a stronger outcome suggesting that the person had no symptoms, no emetic events happening.

Okay, so anyway, there were very few differences…also very few differences in tolerability across the trials. So there was one trial that was fairly good sized in which Ondansetron was associated with significantly higher rates of abnormal vision and dizziness. That was on one of the 20 trials…but there was only one other trial that reported those same outcomes in terms of specific adverse events. The difference in abnormal vision rates was not replicated in that trial but that was also a much smaller trial. But there were no other differences between Granisetron and Ondansetron on any tolerability outcome across the rest of the trails.

And then finally in terms of key question three for this comparison, there was only one of the 20 trials that conducted a subgroup analysis of patients with a predisposition to nausea and vomiting. And interestingly the results suggested that Ondansetron was associated with significantly higher complete response rates than Granisetron in this population. So if you looked in that study, you looked at the population as a whole. There were no differences but specifically in the subgroup, patients with a predisposition to nausea and vomiting, patients responded better to Ondansetron than Granisetron.…IV Dolasetron versus IV Ondansetron. And there were three…only three head to head trials here but two were good quality and so across the three there were no consistent differences between IV Dolasetron and IV Granisetron in the combined outcome of complete response rates within 24 hours and beyond or intolerability across the fair to good quality head to head trials. So as you can see, the only differences in efficacy and in safety came from the fair quality trial but those findings were not supported by the good quality trial. The evidence of no difference is stronger…considered to be stronger than the differences found in the one study. And then for subgroups there were no subgroup analyses reported in any of these three trials.

Next slide, 22. Comparison of IV Dolasetron and IV Granisetron. There was only one head to head trial of these drugs in 474 patients that were mostly men and were receiving highly emetogenic chemotherapy for head, neck malignancies and it was rated good quality. And no differences were found in complete response rates within

24 hours so only the first 24 hours, or in rates of tolerability. And no subgroup analyses reported.

Okay, slide 23. Palonosetron. So Palonosetron was studied in two fair quality head to head trials and so overall patients in these trials were predominantly female, 77% were female and were primarily undergoing moderately emetogenic chemotherapy for breast cancer. In these trials, Palonosetron was associated with significantly higher complete response rate at 24 hours and between days two and five when compared to either Dolasetron or Ondansetron and the table reflects the numbers needed to treat by Palonosetron for one additional patient to achieve a complete response. And I also wanted to note that results of an unpublished trial of patients of 223 patients undergoing highly emetogenic chemotherapy was identified on the FDA web site suggesting that Palonosetron was associated with similar complete response rates relative to Ondansetron. It seems that Palonosetron is superior in the population of patients undergoing moderately emetogenic chemotherapy, but in the unpublished trial which we haven't seen…we don't have access to the full description of the methods so we don't know about the quality, but the preliminary results suggest that Palonosetron has similar results…similar effects on preventing nausea and vomiting in patients undergoing highly emetogenic chemotherapy as does Ondansetron.

Okay, next slide, 24. So there is just this one small trial of Granisetron comparing the IV and oral formulations. This trial was conducted in 60 patients that were mostly female that were undergoing moderately to highly emetogenic chemotherapy as a conditioning regimen for progenitor cell transplantation or bone marrow transplantation. The results from this trial suggest that complete 24 hour response rates and tolerability were similar for the oral and IV forms of Granisetron.

Next slide. Okay, so now we're onto the evidence in children. Again, there is a smaller body of evidence of focus on the study of the effects of these drugs in children. In fact, there were only two head to head trials included that address the prevention of nausea and vomiting related to chemotherapy in children and this table provides some associated details. So the first trial in the table involved 428 children with a variety of malignancies that received loading doses of either IV Ondansetron or Ondansetron syrup, both plus oral dexamethasone 20 minutes before each of eight courses of moderately to highly emetogenic chemotherapy and then all patients also received Ondansetron syrup plus oral dexamethasone six to eight hours after each course of chemotherapy. And in this trial there were no significant differences in rates of patients with no vomits or retches within 24 hours after chemotherapy or on the first day or on the worst day of eight days of the moderately to highly emetogenic chemotherapy. And there were also no differences on the worst day of the whole treatment period which also encompassed the two days immediately following cessation of the moderately to highly emetogenic chemotherapy in which patients were then receiving either no or only mildly emetogenic chemotherapy. And there were no differences in tolerability in this study.

And the second trial involved 90 adolescents with osteosarcoma of extremity and evaluated the comparative efficacy of IV Granisetron and IV Ondansetron given with…both given with IV dexamethasone to control emesis within the first 24 hours after highly emetogenic chemotherapy. There were no differences between

Granisetron and Ondansetron in the rates of patients with vomiting or retching and adverse effects were not reported. So please note the type-o in this slide in the outcomes columns for the second study. The equal symbol should be in the 24 hour column and the not reported abbreviation should be in the greater than 24 hours column. Because this study only measured outcomes within the first 24 hours and during that time there were no differences between the drugs.

Okay, next slide, 26. So we're going to switch gears now and look at the evidence from trials of the prevention of nausea and vomiting that are associated with radiation. And there were a limited number of trials in this area and none compared anti emetics head to head. So in adults there was only one trial that involved Granisetron and Ondansetron. So there was the potential for making direct comparisons there, but instead each was compared respectively to a historical control group and not to each other. So it's a trial that we can only infer indirect comparisons from. And so the historical control group was patients that underwent total body irradiation in 1991 and that were matched to the patients who were given Granisetron matched for age, disease diagnosis, radiation…and radiation regimen, but that were not given Granisetron or Ondansetron. But there was no information about what anti emetics that they may have been given. So they probably were given other type of anti emetics. So it's probably more like an active control comparison.

In any case, the patients in this trial were all undergoing total body irradiation and in this trial Granisetron was associated with significantly higher complete response rates on day zero and in days one through four, whereas Ondansetron at lower than recommended dosages was associated with similar complete control rates. Similar complete control rates to the historical control group at day zero and then those affects became significantly greater than in the historical control group during days one through four. So, again, it looks like there is a disparity in effects on that day zero but you have to keep in mind that Ondansetron was dosed at lower than recommended dosages. So it's not…I don't know that that's a fair indirect comparison to make between those drugs on day zero. We did try to look at placebo and active controlled trials for indirect comparisons between any drugs in this population of patients undergoing radiation, but found too much heterogeneity in patient populations, radio therapy regimen comparators and outcome reporting methods. And then we also didn't find any eligible studies in children undergoing radiation. So it's just the one trial that we can really analyze results from and even then there's a possible dosage disparity issue.

Okay, next slide, 27. And so this is a slide that summarizes results …summarizes evidence for the prevention of nausea…or treatment of nausea and vomiting associated with pregnancy. And we only found one active controlled trial of Ondansetron and in this trial Ondansetron and Promethazine were similarly effective on all outcome measures in 30 women that were hospitalized for hyperemesis gravidarum. And then we also found an observational study of 176 women in which there were no differences in live births, number of malformation, birth weight or gestational age at birth that were associated with either Ondansetron or other anti emetic drugs used following exposure during gestational weeks 5-9.

Next slide, 28. So in the next four slides I tried to pull together all the evidence across all the populations. So the message of this slide is that Dolasetron, Granisetron, and Ondansetron are the most widely studied, newer anti emetics and there is no consistent evidence that any of these anti emetics are superior in efficacy or safety than any other when used in adults for prophylaxis of nausea and vomiting associated with surgical procedures or chemotherapy or when used as treatment of nausea and vomiting associated with surgical procedures. And then further, Granisetron and Ondansetron are also associated with similar effects when used as prophylaxis of nausea and vomiting associated with radiation. And then finally Ondansetron was the only one among these three anti emetics to be associated with improved quality of life outcomes relative to placebo. So there seems to be no consistent evidence that any of these drugs are superior but there are differences in the sense of Ondansetron as associated with more evidence and covering a broader range…therapeutic range and then Granisetron is sort of second tier and then Dolasetron is third. But no evidence that any is superior.

Next slide, 29. This summarizes the main findings for Dolasetron, Granisetron and Ondansetron relative to children. Like I said, there were fewer trials in children and they again only involved those three anti emetics and, again, there was no consistent evidence that any of them were associated with superior efficacy or safety than any other. So, again, the only differences are that Ondansetron has been studied in head to head trials in children undergoing surgical procedures or chemotherapy whereas the evidence for Dolasetron pertains only to children undergoing surgical procedures and the evidence for Granisetron pertains only to children undergoing chemotherapy. So the populations that these drugs have been studied in are different across the three drugs.

Next slide 30. This slide pertains to the evidence for Palonosetron and so Palonosetron is the only newer anti emetic that has been associated with complete response rates and quality of life outcomes on day one that were consistently superior to both Dolasetron and Ondansetron in efficacy and similar in safety in the two trials in patients undergoing moderately emetogenic chemotherapy. And then I wanted to put out there that the total numbers of patients in these trials were actually 380 in the trial of Dolasetron and 374 in the trial of Ondansetron and I'm noting this type-o, just another type-o, sorry, that I notice the sample sizes I listed in these slides pertain only to the Ondansetron and Dolasetron arm of the two studies. So just a point of accuracy there, it doesn't change the results.

Okay, next slide, 31. Evidence for Aprepitant. So evidence for Aprepitant is limited at this time. Presently there are no fully published head to head trials. The makers of Aprepitant have indicated that there is a trial that has been conducted that compared Aprepitant to Ondansetron and that results are available currently in conference proceeding form. We will make a note of that and we will look forward to the fully published report of this trial. So what we did have were numerous placebo controlled trials of Aprepitant used as both mono therapy and combination therapy and we included these in our review and they consistently suggested that Aprepitant was superior to placebo in the treatment of patients undergoing chemotherapy.

Next slide, 32. This is just a final slide here. Just identifying some gaps in the evidence that we saw that would be areas for future research and those as usual there was a shortage of evidence in children and there was a shortage of evidence using more real life outcomes like quality of life and resource utilization. And then as usual there was a shortage of evidence in subgroups. So there is a need for more head to head trials, for comparisons other than Granisetron and Ondansetron and especially for Aprepitant.

Okay, so last slide. That concludes my comments related to the final report of our drug class review of the newer anti emetics. Thank you, and what questions do you have?

Man: Thanks, Kim. That's what we're going to do right now, is just open it up to P&T committee members for questions on your presentation.

Kim Peterson, MS: Okay.

Vyn Reese, MD: Hi, this is Dr. Reese. I had a question about Palonosetron. It's being effective in moderately emetogenic chemotherapy as better than the comparator drugs, but in highly emetogenic chemotherapy in a published trial it's the same as Ondansetron. Do you have any comments about that, or have you not had a chance to dissect the data in the unpublished trial?

Kim Peterson, MS: That's correct.

Vyn Reese, MD: How do you explain that discrepancy?

Kim Peterson, MS: We can't comment on the discrepancy until the fully published report is made available which will provide a full description of the methods. So we haven't been able to assess the quality of the methodology, so we really can't make a comment on how much…how valid the results are and then also why they are not consistent with the evidence in the patients with …undergoing moderately emetogenic chemotherapy.

Man: Other questions here?

Patti Varley, ARNP: This is Patti Varley. Just for point of clarification, when most of the research is done of the three, and for pronunciation purposes [inaudible] but the references you made quite often and just when we were looking at it about dosage comparisons. I guess as you look at those three agents in the comparison trials between the three which have the most evidence, would the adjustment of appropriate dosaging necessarily change what you would see as the outcome at this point or not?

Kim Peterson, MS: I'm sorry, I'm having trouble hearing you. Can you repeat the last part of your question or the main point of your question?

Patti Varley, ARNP: I guess the main point of my question has to do with the three main medications that have the most data when all is said and done, don't look much different one from the other.

Kim Peterson, MS: Right.

Patti Varley, ARNP: But you made reference, and I noticed throughout, that there were times when the dosage comparison put it in a place where it made it hard to really assess that data. And I guess I'm just wondering your opinion that if you were to adjust for appropriate dosaging of comparing those three meds would it have changed the end result in your mind?

Kim Peterson, MS: Well, it's a question. So, yes, we noticed the dosage disparities and all we could stay is in these studies there was no clear pattern of…if one drug was dosed at a higher range relative to the other across and if that was also the case in another study. There was no clear pattern of well if this drug is dosed higher and this drug is dosed lower then all the time it shows that they're the same versus one in which the drugs were dosed comparably. So we looked at that and tried to make sense of it and we really weren't able to draw any conclusions about it and…but we do note that that's a question and we note that that was an observation that we made.

Patti Varley, ARNP: So it didn't come out that…I guess the way that I'm thinking about it is the subtle differences that we're seeing in some of the comparisons of quality of life or this response versus that response, it couldn't be explained by the dosage offset along which would make one in one study look a little better than the other. That wasn't the consistent…

Kim Peterson, MS: Well, if we're talking about the where we wanted to try to make indirect comparisons across placebo controlled trials and we noticed that I think there was a case in which there were, say, three placebo controlled trials of Ondansetron and in those trials Ondansetron was superior to placebo in improving quality of life, however, and then when you looked at a comparable trial of Granisetron and it didn't …it's effects were no different than placebo and we noticed that the dosages were different, like we either didn't know if they were appropriate or we thought that they were relatively lower, we were cautious about interpreting those results and didn't make conclusions and would encourage others not to make conclusions from those because of the dosage disparities. Now, in the head to head trials, there were numerous and the dosages were not always comparable, levels I mean, but we saw no clear pattern that we could make any inferences about that…maybe that they were the same because drug X was always dosed higher…relatively higher than drug Y. So there wasn't…we didn't see anything…we looked for that and didn't see anything like that and so didn't make any conclusions about it.

Patti Varley, ARNP: Thank you.

Janet Kelly, Pharm D: Kim, this is Janet Kelly. I have a question about the timing of the nausea and vomiting. It looks like most of these studies we are talking about acute nausea and vomiting and not delayed. Is that correct? Is there any data about delayed nausea and vomiting with these agents?

Kim Peterson, MS: In some of the trials, I mean yes. In most of the trials they were focusing on the effects in the first 24 hours and when you say delayed, I don't know if you mean what period you mean, but there were also many that reported…they would just say that it

was beyond 24 hours. So refer to that as being delayed with just after the first 24 hours as being delayed versus acute. So there were trials that reported rates during that time period. And other trials wee more specific. They would specify days two through five, for example. And maybe you can comment on whether…when you say delayed, is that the time period you mean?

Janet Kelly, Pharm D: I think in general when we are talking about delay it's anything over 24 hours.

Kim Peterson, MS: Yes, there were trials.

Janet Kelly, Pharm D: I'm not getting a sense from looking at this, but they all seem very similar when you look at acute nausea and vomiting but I'm not getting as big of a sense that there is enough comparative here for delayed nausea and vomiting.

Kim Peterson, MS: Okay, so in chemotherapy for example, in slide 20 where the large body of evidence is, the comparison of Granisetron versus Ondansetron, those trials did report complete response rates both within the first 24 hours and then beyond 24 hours, so delayed, if you can interpret that as being beyond 24 hours. There were only a few trials that didn't, like on slide 22 the comparison between IV Dolasetron and Granisetron, they only looked at the first 24 hours. I think there was the one trial in children and in which the type-o is in, it's actually adolescent. The comparison of IV Granisetron and Ondansetron, looked at only the first 24 hours versus the period beyond that. So there are a handful of trials that did not report on the period beyond 24 hours, but the majority did. There were no differences during that time as well.

Man: Other questions?

Ken Wiscomb, PA-C: Ken Wiscomb. Other than the study about nausea and vomiting associated with pregnancy where they looked at Ondansetron versus Promethazine, were there any other studies that looked at Promethazine compared to anti emetics in this category, for example…?

Kim Peterson, MS: I think I heard your question as are there other studies that looked at Promethazine versus other of the newer anti emetics that are included in this review? Is that the question:

Ken Wiscomb, PA-C: That's correct.

Kim Peterson, MS: Okay. There's actually just no other studies, period. No trials that we found, no published trials that we found and there was part of a systematic review also confirmed that that review group had not found any trials either. In fact, interestingly, our searches missed that trial of Ondansetron versus Promethazine and the way that we discovered it was in this other systematic review and it was the review of the one study as being the only trial that's available. So to our knowledge, and if others know of other studies, please let us know. But to our knowledge that is the only trial.

Man: Other questions for subcommittee members? Okay, Kim if you could stay with us for us just a few minutes longer, we're going to open it up for stakeholder comment and

then sometimes after that there are some additional questions that arise. We have three people signed up so we're looking at about 10 minutes or so.

Kim Peterson, MS: Okay, that sounds great.

Man: Okay, thank you. So first is Dr. Kaiser and I ask that you identify your sponsor here with anybody and limit your comments to three minutes, please.

Dr. Kaiser: Thank you. Good afternoon, I'm Dr. Fran Kaiser. I'm the executive medical director with Merck and Company. I'm a clinical professor of medicine at the University of Texas Southwestern Medical Center and an adjunct professor of medicine at St. Louis University. I'm here to speak about Emend and perhaps clarify some issues about Aprepitant.

Emend is the first and only agent in a new class of substance being neurokinin receptor antagonists. It has no other therapeutic equivalent whatsoever. It is a very high affinity, competitive antagonist for substance P neurokinin receptors with little or no other affinity for other agents that have been thought of as being pathophysiologic in nausea and vomiting such as Dopamine 5H23.

One of the recognitions of this unique class is the very recent change in the US [inaudible] where they have carved out Emend as a separate category of anti emetic. It is no longer lumped together with others and it is certainly not appropriate to consider it with the five HG3 antagonists. It has a totally different mode of action and because of that unique mode of action, the USP has changed the categorization of anti emetic agents.

Emend is indicated in combination with other anti emetic agents for the prevention of those acute and delayed nausea and vomiting that can be induced by both moderately and highly emetogenic chemo therapeutic agents. The gold standard in chemo is something like this class. And when that is used as an inciting agent for nausea and vomiting, being efficacious under that circumstance is very powerful as Emend is, but it is not a stand-alone. It is an add-on therapy, and for that reason the way the EPC questions or frames, it is very difficult to make appropriate comparisons with the other agents being considered in this class. And, again we think that may not be the best way to take a look at this agent which is unique.

There are data available on Emend. Many of those, unfortunately because of the newness of the drug, were submitted following the cut-off point for the EPC, but there are certainly quality of life data and they are included within our package insert. And they are available if one reads the PR. So quality of life patient reported outcomes, which are very positive for Emend compared to other agents such as Ondansetron with dexamethasone are available just within the body of PR.

Again, we respectfully request and strongly encourage that you consider Aprepitant as a separate category of anti emetics following the USP categorization as a separate class of drugs within anti emetics. And we're concerned that perhaps the way this is being reviewed today that patients may not be able to get the benefits from the

debilitating effects of nausea and vomiting due to chemotherapy if Emend is not considered as part of the regimen. Thank you for your time.

Man: Thank you. Are there any questions? Thank you. Next is Dr. Cherry?

Nancy Cherry: Good afternoon, my name is Nancy Cherry. And I'm with Glaxo Smith Kline, an oncology medical scientist for Glaxo Smith Kline. I'm here to speak to you today about Zofran. I believe that there is a significant amount of data that is not clearly explained in the Oregon Report. I think the easiest way to look at this is to divide it into two categories, the first amount of data that is in…with the use of oral use of these drugs, and secondly with the IV use of these drugs.

Regarding the oral use of these drugs, there are two points that are not well elucidated and the first point was something that Dr. Kelly addressed. And that is the use of Zofran for delayed nausea and vomiting, or nausea and vomiting that occurs on day two or day three. And it's not yet…it's not really…you're not really able to just look at the responses. You also need to look at the trials that actually dose the drug on day two and day three. Not all of these trials did that. Zofran is the only compound in the short acting [inaudible] antagonists, that is Kytril, Anzemet and Zofran. Of these three agents, Zofran is the only agent that is FDA approved to treat chemotherapy…or to treat nausea and vomiting that occurs on these delayed phase day two and day three. This is an important point that is not addressed in the OHSU report.

Secondly is the unique formulation of the orally disintegrating tables that Zofran has and no other anti emetic has this formulation. This orally disintegrating tablet, which is placed in the patient's mouth, dissolves in the mouth, allows patients who are so nauseated or vomiting so severely and they cannot actually swallow a tablet, gives them an additional choice and gives their physician an additional choice to help individualize therapy to their individual patient's needs.

Then when we move to IV usage of these drugs, it's very important to note that in the single trial…single published trial of Palonosetron or Aloxi versus Zofran that Dr. Reese indicated, there are very conflicting data. We believe, and if you were to look at the actual trail which shows…portends to show significance, there are significant flaws in this trial which I'd be happy to explain later if you'd like. These significant flaws in the design of this trial are what lead to their proposed significant outcome which then later is not supported by their unpublished trial. It's also important to note that the unpublished trial was sponsored by the pharmaceutical company MGI that makes Aloxi which may be why it's not been published yet.

And lastly, when we look at these drugs for the use in not just chemotherapy induced nausea and vomiting, but also postoperative nausea and vomiting, which is where about two-thirds of the usage of this drug is in the postoperative setting. Palonosetron or Aloxi is not…is really not indicated and really has no role at all yet in the treatment or prevention of postoperative nausea and vomiting. I believe this is an important point that is not reflected in the OHSU report and you need to have this information before you can make this indication.

And lastly I'd just like to touch on the safety profile of Zofran as safety is not brought up. Unlike Anzemet, we do not have a black box warning. Anzemet has a black box warning for QTC prolongation. Zofran does not have that. And we have been on the market the longest, since 1991, have treated over 125 million patient treatments. That's about four times greater number of patients than the other anti emetics have treated and if there were a rare side effect, we would be more likely to see it. Thank you very much.

Man: Thank you. Any questions? Finally, I think this is Monica Marcus, or Dr. Marcus, is that it? Marcu, I'm sorry.

Dr. Marcu: Hello, thank you very much for giving the opportunity to talk about Granisetron or Kytril. I'm Monica Marcu. I have a Ph.D. in molecular pharmacology and a PharmD degree. My medical is on [inaudible] since 2004 and I came from National Institutes of Health where I used to be a scientist.

Kytril, as you know, is approved both for adults and for pediatric uses for children older than two and is very well tolerated in children and adults. It is indicated for chemotherapy induced nausea and vomiting, radiotherapy induced nausea and vomiting and postoperative nausea and vomiting.

Granisetron injection is FDA approved not only for prevention but also for the treatment of the [inaudible]. All the studies have shown that Kytril is very well tolerated. Even in elderly with [inaudible] and concomitant medications which one of these is actually to be addressed in the future, but we have some studies about Kytril in this concomitant medicated patients. It's very well tolerated in renal failure and hepatic impairment. Therefore there is no need for adjusting the dose of Kytril and leaves quite a lot of flexibility to the medical care giver.

In terms of metabolism, also the OHSU report does not address this. There are significant differences between the way this agent is metabolized and the probability of side effects. Kytril does not induce or inhibit the cytochrome p450, presents the lowest risk of drug interactions. Granisetron has a different and specific metabolic pathway compared with the other [inaudible] inhibitors involving enzymes that are not used by the majority of other pharmacologic agents known.

All the metabolic differences between Kytril and other agents in the class can translate into pharmaco-economic benefits and advantages both for patients but also for the caregiver. The adverse events reported with Kytril are generally mild to moderate. No clinical significant cardiovascular risks exist.

In terms of efficacy, studies have shown that with equal doses of Granisetron and Ondansetron for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, this agent showed equal efficacy but there was less significance…sorry, there was less [inaudible] abnormal vision with Kytril compared with Ondansetron among others.

The clinical studies have shown that Granisetron has significant efficacy, tolerability in high dose chemotherapy or total body radiation for bone marrow transplantation and also for particular blood stem cell transplantation.

I would like to conclude…and the studies have shown…the report has shown that most of the studies we have show that at equivalent doses of 5HT3 antagonists have equal efficacy as anti emetics as far as we know now. But also studies and reports have generally concluded that the agent with the lowest risk of potential drug interactions should be the primary choice when considering anti emetic treatments for chemo or radio therapy or surgical procedures. As far as we know, Kytril has the lowest risk of potential drug interaction and is very well tolerated in adults and children. Thank you very much.

Man: Thank you. Any questions? And Kim, are you there?

Kim Peterson, MS: Yes.

Man: Okay. I think there might be a couple of questions her for you.

Kim Peterson, MS: Okay.

Man: Kim, it's hard to know were Emend fits in this group. It seems like it's mainly indicated for markedly delayed nausea and vomiting. How do you see Emend and are the studies adequate…they are included in your review, to tell us what to do with Emend?

Kim Peterson, MS: Yeah, I mean I agree that it seems to be used differently. I mean that came out in the evidence in terms of there being…it's being used as primarily add on therapy and we included placebo controlled trials and there are no head to head trials and so we…and this has come up before, it's been said that it's like comparing apples and oranges, putting Emend in this category. And that may be the case. It may…I think it needs to be up to the purchase…the DERP participation organizations as to whether it should stay in this drug glass review. Our focus is always on clinical efficacy and so if there were to be a head to head trial, which I was told that there was a head to head trial of Aprepitant versus Ondansetron, that we would look at the comparative clinical efficacy there and it would be appropriate to do so given that the usages would be studied…the similar usages of those two drugs would be studied in a single head to head trial. Until that time that those results are made available, we really just can't comment. All we can say is that in these placebo controlled studies Aprepitant is superior to placebo when used as add-on therapy and that there were no other studies of any of the 5HT3 antagonists that were uses as add-on therapy and so the evidence just does seem to be different.

As to telling you what to do with that, I'm not supposed to do that. You'll have to think about how it's…how your constituency uses the drugs and whether Aprepitant, that usage is necessary.

Man: Other…not right now, thanks. Other questions?

Patti Varley, ARNP: This is Patti Varley. I have two questions. One is I'm looking at the different agents. There was a mention of the oral disintegrating tablets. Are there different forms of the…for route of administration between these drugs? I just don't use them enough to know as far as availability amongst them. And then my second question has to do with is there any evidence or data about each of these medications in regards to history of drug/drug interaction?

Kim Peterson, MS: Okay, first question, are there differences in the drugs in terms of the formulations that are available. And the answer is yes. At the present time, to our knowledge, Aprepitant is available only as an oral form and Palonosetron is available only as an IV form. And then the other three, Dolasetron, Granisetron and Ondansetron are available in both IV and oral forms with Ondansetron having the oral disintegrating tablet as well. So there are differences there.

And then the second question was did we find any studies related to the differential effects of these drugs with regard to drug/drug interaction. I think that was your question. And the answer is no.

Man: I had a question about Granisetron and I believe there was a comment in the stakeholder input relative to this particular medication not being renally cleared.

Kim Peterson, MS: Not being what, I'm sorry?

Man: Renally cleared. Is that correct? And are the others…how are the other cleared, metabolized?

Kim Peterson, MS: That's something that is somewhat…in terms of the mechanism of action and pharmacokinetics is outside of the scope of this review in the sense that our focus is on clinical outcomes so what we would look for would be evidence of the adverse effects of the clearance and didn't find any evidence of serious adverse effects that were of fair or good quality to include. I would say that we can't comment from an evidence perspective in that…in terms of the effects on clinical adverse effects.

Man: Do you know if any of the drugs are specifically contraindicated in renal insufficiency?

Kim Peterson, MS: I don't. I don't know.

Woman: No.

Man: No, thank you. Other questions?

Angelo Ballasiotes, Pharm D: May I ask Siri a question with regards to Emend. Do you know the usage of that? [inaudible]. Do you have it written down or on the computer?

[inaudible]

Man: Is that how you see it used?

[inaudible]

Man: In terms of Emend…

Kim: We will be discussing this class soon in our monthly meeting of our drug [inaudible] review projects. And we will be going over starting the key questions for the next update. So we will bring that up at that time.

Daniel Lessler, MD: [inaudible]?

Female: [inaudible].

Daniel Lessler, MD: Right. Clearly. Other questions for Kim while we still have her on the phone at this point? Points of clarification?

Patti Varley, ARNP: Patti Varley again. Just because it was mentioned again and the testimony had to do with the OTC labeling on [inaudible] and not the others. Can you comment on that please?

Kim: Well, I think that that is something that you should think about. And in terms of the context of our review we've looked for the evidence that would support that black box warning and didn't find it. And so we would note that it has the black box warning, but from evidence perspective really can't comment further than that. But I think, you know, that is something that I think I agree that would be good for your committee to think about as well as the other things mentioned by Dr. Cherry with Glaxo-Smith Kline that Ondansetron doesn't have the black box warning, you know, it has more indications than the other drugs, different formulations. Those are things that I think that is important for you to hear and think about, but those are things that are outside of the scope of the report unless they are translated into evidence. So we didn't find evidence of any drugs being more or less safe than the others.

Daniel Lessler, MD: Okay. Any other any other questions? All right, Kim. Thank you very much.

Kim: Oh, you're welcome. Thanks. Bye.

Daniel Lessler, MD: Bye. And so, again, just wanted to see if there's some general comment or observations just to get us thinking here and perhaps moving towards some decision. Tom?

Tom: Hi, [inaudible]. So when it comes to DSHS, do we need to consider Palonosetron because it's only IV and would probably be administered in the clinic or hospital? Would it be safe to just not include that? Or to include it even though it's not going to be used on an outpatient type basis?

Daniel Lessler, MD: Siri, you need to talk into the mic, please.

Siri Childs, Pharm D: I am amazed because we do get requests [inaudible]. And I don't know why. I guess maybe some of the [inaudible] centers are billing [inaudible]. And we do love that because then we get rebates [inaudible].

Tom: Okay. So the patients are taking the drug and self-administering it?

Male: They're picking it up there and taking it to their doctor.

Tom: Taking it to their doctor's office.

Siri Childs, Pharm D: Or, they are part of a cancer treatment center where the pharmacist and [inaudible] work with the nurses and they actually administer the drug in the [inaudible] setting [inaudible].

Daniel Lessler, MD: Other...does anybody have any kind of framework that they want to maybe put out there just to how we might go about thinking about this class of medicine?

Robert Bray, MD: Bob Bray. I...the way I see the evidence presented, it seems like it's easier to divide these drugs up as adult drugs and pads drugs because there's gonna be a difference. So it seems to me that the three drugs; Dolasetron, Granisetron, Ondansetron would allow us to have a number of drugs that have the maximum indications and have both IV and PO administration routes. And in kids Dolasetron and Ondansetron do the same, where they have the maximum amount of medications and have both IV and PO routes of administration available. So I haven't crafted that into a proposal, but I guess that would be a reasonable way of approaching that.

Male: So, for example, an adult saying Dolasetron, Granisetron and Ondansetron are safe and efficacious...and just leaving it at that 'cause there's really not...actually for the most part you're almost [inaudible] equal and often and that would be the motion...or that would be where we were headed.

Male: The intent of the motion.

Male: Right. And then something similar with the two drugs for children. It seems like with amend, I don't think we can comment on it here one way or another it's gonna probably need to be dealt with the way it's being dealt with. It doesn't really fit in here contextually.

Patti Varley, ARNP: Patti Varley. And just for point of discussion. Based on the point that was just made. Why would you not just have Kytril and Zofran and leave out the other ones if the other two for adults and kids have evidence and don't have the QTC risks?

Robert Bray, MD: Bob Bray. I guess the way I'm thinking about it is that the evidence does not show a clear drug that's safer or less safe. And I think that the QTC thing is such a difficult problem to try to be eliminated...if we automatically eliminate the drugs that have any kind of QTC problem we'd be eliminating a lot of drugs. And so from my standpoint, I think if the evidence doesn't show that one drug is safer or less safe, I would be comfortable including that in the [inaudible].

T. **Vyn Reese, MD:** Dr. Reese. I have a question about what...we're talking about the big three in the middle that we have more data on. Palonosetron has not a lot of data, but the data we do has it looks positive. So I don't know whether we...plus its indications are less. It's not indicated in post operative nausea vomiting or radiation therapy. So it's a very limited spectrum. I think I agree that Emend just doesn't fit in this group. I don't know what to do with it. So those are all things to think about. I don't know whether we have to say that certain formulations are for children or adults or we can sort of generally say this is the group. And I think we can let the body make the final decision. Decide if a drug is able to be given to kids or not. And if there's an oral formulation.

Robert Bray, MD: Bob Bray. I guess my...the only clarifying point I'd make about Kytril is that although it had a pediatric indication it has only 1 approved route of therapy, and so I would just want to avoid a situation where that could be chosen as one that would be the only one that has a pediatric indication but now we have only one route to give. So that's the one of the things…

Male: We could add that there needs to be a pediatric oral product.

Jeff Graham, MD: Jeff Graham. We did that in other classes we've done.

Alvin Goo, Pharm D: It's Alvin. Looking at this review it kind of seems that [inaudible] for the agent that has the most difficult route it would be Ondansetron. And [inaudible] the first one that came up...all the studies sort of compare themselves to Ondansetron and there's really no difference. So although I think you're right, we need to consider the [inaudible] population [inaudible].

Daniel Lessler, MD: Other thoughts?

Jeff Graham, MD: This is Jeff Graham again. In other drug classes we named several drugs within that class that you felt were safe and efficacious and then you've given the department the responsibility to make the decision.

Male: And I think that's generally the way we should go, and I appreciate Alvin's comments and agree, but I think what we want to try and sort of do is specify whether something is...looking at the evidence, if it's safe, efficacious, either independently or comparatively and so forth. So I'm actually going back to where we were at. I'm wondering if...I can't remember now whether...I think, Ben, it was you were thinking about sort of just combining them and then specifying that an oral agent that's approved for kids, right. So, I'm wondering if…

Male: [inaudible].

Male: Yeah. You might be willing to craft something we could look at at this point just to…

Robert Bray, MD: Sure. Okay. This is Bob Bray. So after considering the evidence of safety, efficacy and special populations for the treatment of nausea and vomiting related to chemotherapy, radiation therapy and post operatively, I move that Dolasetron,

Granisetron and Ondansetron are safe and efficacious. No single newer antiemetic medication is associated with fewer adverse events in special populations. At the end of that sentence I would add the PDL must include at least one medication that has both oral and IV routes that are approved in both adults and children. We haven't discussed the part about the...hang on. We haven't discussed the thought...the issue about therapeutic interchange and I guess I would say that we would say that they could be. Can.

Daniel Lessler, MD: Okay. That gets us started. Let's just see if anybody wants to comment on that or if there are further suggestions on how to modify this.

Patti Varley, ARNP: This is Patti Varley. And I'm confused because when I was listening to the data presented with the head-to-head trials involving kids, I saw...and maybe I'm wrong, but there wasn't strong evidence one way or the other, but there was at least some minor but it was not in the medication...it wasn't in the Dolasetron it was in the other two. And I'm just a bit curious in your mind when you were saying one was preferred in kids, where's the evidence for that? Or what one is it?

Male: You're asking me the question?

Jeff Graham, MD: This is Jeff Graham. I think it was the two drugs. It didn't say one was. It just said there were two drugs that I believe are...there was no difference. So and we've got three drugs up there so what I think they're telling us is that we need to have at least one of those two drugs for children.

Male: Slide 25.

Robert Bray, MD: One of the...this is Bob Bray again. One of the breakers here is that with Granisetron it would not be considered...it may not be considered in pediatrics because of the fact that it does not have an oral formulation, an approved oral formulation for kids. And so that would leave...so sort of by default that leaves Dolasetron and Ondansetron as the available drugs for kids.

Daniel Lessler, MD: Right. It doesn't...it does not have an approved oral formulation in children, at least according to the summary report.

Robert Bray, MD: Does that...I'm not sure whether that addresses the question you're having. Okay.

Daniel Lessler, MD: Are there any other comments on constructing a motion that looks something like this? I don't know if anybody...any particular concerns about it or-.

Patti Varley, ARNP: This is Patti Varley again. I'm sorry. I still...Jeff, on looking at this and even though it wasn't part of the evidence base it's part of our information, just like it's part of our information on what's FDA approved for kids or not, is the QTC thing. And I'm stuck on it a bit.

Jeff Graham, MD: Stuck on...they're not all approved for all of those things by the FDA. Anzemet's not approved for post radiation therapy nausea and vomiting where Granisetron and Ondansetron are. So that's not FDA approved for that indication, even though we're

saying it's equal to the others. So that's not entirely so. We could handle this by just making Granisetron and Ondansetron and then just leave the QTC concern out. QTC concern, I think it's theoretic, but it could be clinical in a small group of patient, it really could. But you're also right that there are multiple drugs with that concern. So it is a concern that it's nice not to have to worry about.

Patti Varley, ARNP: And again...this is Patti Varley again. When I think of that logic, what I think is that sort of again the idea that you pick the safest, most efficacious ones first and then you move on to the others if and when those don't work and you need them. And my logic, that's where that one doesn't fit the other two.

Jeff Graham, MD: So that would leave us with Granisetron and Zofran.

Daniel Lessler, MD: Do we want to make that change...you already did. All right. Okay. Any other any other comments…

Robert Bray, MD: Bob Bray. I just am addressing what Vyn was saying. If we said there's a special population of...well, I guess never mind. You're covering the special population by making sure that Ondansetron's in there so never mind. I was thinking about the post radiation.

Angelo Ballasiotes, Pharm D: Angelo Ballasiotes. Is Emend going to be in this one? Are we going to make a separate motion? Or…

Daniel Lessler, MD: I think we just are going to table...it doesn't belong in the discussion we're having right now. It belongs in a different discussion.

Male: We do need to probably at least list the other two drugs because remember when we've not done that in the past we've come back and asked you what did you want to do with those other two drugs? Do you want to still them to be non-preferred and still include them in the drug class.

Janet Kelly, Pharm D: Janet Kelly. I'm getting...I think we do need to say something about them because when we say about therapeutic interchange it's not appropriate to [inaudible] to Ondansetron. And I think we do need to say something that they are different drugs and that we need to handle them...they're not in that class.

Daniel Lessler, MD: But if they're not on the preferred formulary then they can't be interchanged.

Female: [inaudible] approved as the newer antiemetics. And we need to make it very clear that it doesn't belong in this group.

Patti Varley, ARNP: This is Patti Varley. Can you add a sentence that says Emend should be on the Preferred Drug List but not included under this category?

Daniel Lessler, MD: I don't think we can...so we could add that Zofran and Granisetron are...no, it would be the other way around, it would be…

Robert Bray, MD: This is Bob Bray. I guess from my way of thinking, the drugs that would be potentially therapeutically interchanged would only be the drugs that we mentioned on the Preferred Drug List. And so if they're not on the Preferred Drug List, those drugs could not be interchanged with the drug on the Preferred Drug List, correct?

Jeff Graham, MD: This is Jeff Graham. I know the agencies will come back and ask, Well, what did you mean about Anzemet and what did you mean about Aloxi? Are they non preferred drugs within this class?

Daniel Lessler, MD: So why don't we just state...can we just add then that Anzemet and Aloxi are nonpreferred drugs in this class.

Duane Thurman: This is Duane. The issue that will come up is that this has been reviewed as part of the OHSU review. Two things have to occur before it becomes subject to the dispense as written override provided in the law and that is it has to be included in the review and you need to make some statement on it, and so you do have to remember that the effect of saying if they're in this class they're going to be subject to dispense as written. That's the issue. And so you can say that they're specifically nonpreferred, but if you say that they're not in this class, then they are not subject to that and that causes a consistency problem because they were reviewed as part of this therapeutic class by OHSU. I guess the simplest thing would be, you know, if you want to...if you see this as a class at this point, to simply say that they are nonpreferred.

Female: Just a suggestion that if you want to...I don't know [inaudible].

Daniel Lessler, MD: So could we say that Anzemet and Aloxi are nonpreferred and Emend is...you know, is not part of this class, is not a 5HT antagonist. And I mean, so we're...effectively we don't we just don't want it considered here.

Female: I have one clarification or possibly two. So, I put up here, do you feel then that the Dolasetron and Palonosetron could be interchanged within their [inaudible] administration like an IV for an IV or a PO for a PO? So that...that's one of the things that we're going to run into if these drugs are nonpreferred, can they be interchanged for the preferred drugs that you've selected.

Daniel Lessler, MD: Yes.

Female: Okay. So, are you okay with the final statement that I have here? Remember, if it's in a doctor's office we don't make an interchange.

Daniel Lessler, MD: Well, I'm hearing two different things. I heard from Siri that if it's on a...if we have a Preferred Drug List the only drugs that can be interchanged are the drugs on the Preferred Drug List.

Female: These drugs are on the Preferred Drug List. They are in this class of drugs. You can't say that the Palonosetron and the Dolasetron are not part of the 5HT receptor antagonists. You can say Emend is not because you can say that that's a different mechanism of action, but they are non preferred drugs within this class and we need

instructions on whether or not the non preferred drugs can be interchanged for the preferred ones.

Daniel Lessler, MD: Okay. So my...and I guess I feel that that's the reason we're making them nonpreferred is we do not want them to be interchanged with the drugs from the Preferred Drug List. So we would list the drugs that are on the non...that should be listed non preferred and say that they cannot be subject to therapeutic interchange. Is that what we're talking about?

Male: I think what we're saying is that [inaudible] can be...maybe that's not what we're saying but maybe...I thought what we're saying that the preferred drugs can be interchanged for the other drugs the nonpreferred. But they're all in the same class. We just listed the classes above. Now there may be some reason that somebody writes dispense as written that somebody has been intolerant of the other drugs and has to have Palonosetron or something like that. And that may be dispense as written, and that would be substituted from one of the...you know, that would be a drug that would be given at that point.

Daniel Lessler, MD: But the pharmacist does not substitute that drug, the physician asks for it. I think that's the difference, right? If it's dispense as written. So it's really not an interchange, it's an acknowledgement that it's a dispense as written issue. It's not an interchange.

Male: Well, I think what we're saying is if one of these nonpreferred drugs...if we had Kytril as nonpreferred. A doctor wrote a prescription for that, signed substitution permitted and therapeutic interchange is allowed, then Zofran would be given. Is that a problem? So what we're saying is it could be interchanged, then.

Female: We don't...we don't give nonpreferred drugs in place of preferred drugs. If a nonpreferred drug was prescribed and the endorsing practitioner allows therapeutic interchange, the pharmacist would be allowed to give the preferred drug.

Daniel Lessler, MD: But they couldn't do it the other way.

Male: Good.

Daniel Lessler, MD: Okay. If it was Zofran written, they would not get a nonpreferred drug.

Female: So the last sentence I tried to write that down. That these may be subject to interchange.

Daniel Lessler, MD: Correct.

Patti Varley, ARNP: So...this is Patti Varley. Do we need to say something about Emend in this or not?

Daniel Lessler, MD: I think the problem we're having is it's not in this class. So we can't really force something in where it doesn't belong. It certainly wouldn't be subject to therapeutic interchange, for example. So.

Patti Varley, ARNP: So should we list it as not…

Jeff Graham, MD: This is Jeff Graham. If we list it as nonpreferred and say it is not subject to therapeutic interchange. [inaudible] like in other classes.

Daniel Lessler, MD: So then we can one last sentence which would be that and then is not preferred and is not subject to therapeutic interchange.

Male: Well, I think Siri's saying no, that she'd prefer that it not be in this class.

Daniel Lessler, MD: Or we can just leave it out.

Siri Childs, Pharm D: Leave it out.

Daniel Lessler, MD: I know, it's not a [inaudible]. Okay. So we'll just...and…

Female: Can you say that it's not included in this class and not [inaudible]…

Daniel Lessler, MD: All right. Then we can say that. Why don't we say that it's not included in this class. That's it.

Alvin Goo, Pharm D: Hi, it's Alvin. Should we retitle this instead of Newer Antiemetics just say 5HT3 antagonists?

Daniel Lessler, MD: Good idea. All right. Who...Bob, I think you started with this. You want to just give it one final read through for us?

Robert Bray, MD: Before I do that, just trying to be consistent here, did we not need to specifically state that Dolasetron and Palonosetron are nonpreferred drugs? Did I understand that we were supposed to state that in order to be clear as part of this? And I'm really looking to Siri and Doug and others.

Daniel Lessler, MD: We...it seems that we could do that, it's just a higher level of specificity.

Donna Marshall, Pharm D: This is Donna. I think that the sentence that states that you must have one medication with both oral and intravenous formulations kind of basically says that they won't make it because they don't meet that criteria. So, essentially you're making them nonpreferred with that statement. And it gives us the choice of choosing one or both of the Kytril or Zofran.

Daniel Lessler, MD: But actually you've named them in the class and that's all we need to have you do. Those four drugs have to [inaudible] this class, and that's what you've done.

Female: If you are giving us clear directions that you want us to have specific drugs and you don't want to have other drugs, tell us that. Just...you know, that's up to you. Are you telling us [inaudible]…

Daniel Lessler, MD: I just want to make sure...again, I think we know what we want, but sometimes I have a hard problem interpreting this in the administrative realm of does everybody

else understand did we say what we really mean up here. So what we're saying is that we're identifying two drugs that are safe and efficacious and therefore we wish them to be on the Preferred Drug List, Granisetron and...er, I take that back. That those would be considered in the Preferred Drug List...for the Preferred Drug List. We've given the additional criteria from which to choose. So, by default, it seems like it's pretty clear about what we're saying should be on the Preferred Drug List. I want to make sure we don't have any unintended consequences by what we've said or not or implied.

Male: It would it would seem to me that it would put it to rest if we just said the two agents that are non preferred. I mean, it...again, we can't go wrong then, right. So why don't we write at that point [inaudible].

Daniel Lessler, MD: And then that last sentence, they're interchangeable.

Jeff Graham, MD: This is Jeff Graham. I wanted to make it clear to the stakeholders in the audience that it does not say that either Zofran or Kytril will be preferred. One of those will be preferred, maybe both of them will be. So that...it's clear to us and I'm hoping it's clear to you now. So if only one of them ends up that way, you're gonna come back and say, You told us…

Daniel Lessler, MD: That's correct.

Patti Varley, ARNP: So what we're saying...Patti Varley, is that either one of those, because they come in a PO and IV form and are the safest of the ones with the most evidence of efficacy, would be included. Is that correct?

Daniel Lessler, MD: Either or. Either or both. Right. One or the other or both.

Male: When...just a typo. It should be...in the last sentence it should be the 5AT3 antagonist class. We were talking about that as a class at that point.

Male: Well, I don't read it exactly like it was just interpreted. Way I read it, if I understand the word approved correctly, is one agent of the two that we left that's approved for both routes in children. The way I read our statement is it's saying that Zofran has to be on the formulary and you could also add Kytril as well. That's the way I read it. I don't read it as one or the other.

Male: Right.

Male: But you said one or the other.

Male: But it has…

Male: But not both may make it on there. Well, that's not entirely true. It's going to be Zofran only or it's going to be Zofran and Kytril.

Robert Bray, MD: Let me help here. This is Bob Bray.

Male: And I'm just making sure that that's…

Robert Bray, MD: I suppose one other way we could do this would be in that the sentence that starts the Preferred Drug List must include, we could say the Preferred Drug List must include medication...and you could put parentheses s behind that, that have oral and intravenous routes proved in both adults and children. So then we're not...does that help a little bit if we said it that way?

Daniel Lessler, MD: I think we're fine the way we had it before.

Robert Bray, MD: Okay. Go back the way it was.

Daniel Lessler, MD: You know, we've covered all the bases. I think Jason's right in terms of, you know, technically what it's saying.

Male: Shall we read it?

Male: Please.

Daniel Lessler, MD: So this is the motion and then we can do it formally. Go ahead.

Male: After considering the evidence of safety, efficacy, and special populations for the treatment of nausea and vomiting related to chemotherapy, radiation therapy and postoperatively, I move that Granisetron and Ondansetron are safe and efficacious. No single 5HT3 antagonist medication is associated with fewer adverse events in special populations. The Preferred Drug List must include at least one medication that has both oral and intravenous routes approved in both adults and children. Dolasetron and Palonosetron are to be Nonpreferred. Dolasetron, Granisetron, Ondansetron, Palonosetron can be subject to therapeutic interchange within their routes of administration in the Washington Preferred Drug List. Aprepitant is not to be included in the 5HT3 antagonist class.

Daniel Lessler, MD: All right. We have a second. Is there any more discussion? Good. So why don't we vote. All those in favor say Aye.

Many: Aye.

Daniel Lessler, MD: Opposed same sign. All right. Thank you. So I think that, Jeff, there's no other business?

Jeff Graham, MD: Correct. We will see you back here on April 19th.

Daniel Lessler, MD: Okay. We're adjourned. Thank you.